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Hepatic late adverse effects after antineoplastic treatment for childhood cancer (Review)

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[Intervention Review]

Hepatic late adverse effects after antineoplastic treatment for childhood cancer

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ABSTRACT

Background

Survival rates have greatly improved as a result of more effective treatments for childhood cancer. Unfortunately, the improved prognosis has been accompanied by the occurrence of late, treatment-related complications. Liver complications are common during and soon after treatment for childhood cancer. However, among long-term childhood cancer survivors, the risk of hepatic late adverse effects is largely unknown. To make informed decisions about future cancer treatment and follow-up policies, it is important to know the risk of, and associated risk factors for, hepatic late adverse effects. This review is an update of a previously published Cochrane review.

Objectives

To evaluate all the existing evidence on the association between antineoplastic treatment (that is, chemotherapy, radiotherapy involving the liver, surgery involving the liver and BMT) for childhood cancer and hepatic late adverse effects.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2018, Issue 1), MEDLINE (1966 to January 2018) and Embase (1980 to January 2018). In addition, we searched reference lists of relevant articles and scanned the conference proceedings of the International Society of Paediatric Oncology (SIOP) (from 2005 to 2017) and American Society of Pediatric Hematology/Oncology (ASPHO) (from 2013 to 2018) electronically.

Selection criteria

All studies, except case reports, case series, and studies including fewer than 10 patients that examined the association between antineoplastic treatment for childhood cancer (aged 18 years or less at diagnosis) and hepatic late adverse effects (one year or more after the end of treatment).

Data collection and analysis

Two review authors independently performed the study selection and 'risk of bias' assessment. The 'risk of bias' assessment was based on earlier checklists for observational studies. For the original version of the review, two review authors independently performed data extraction. For the update of the review, the data extraction was performed by one reviewer and checked by another reviewer.

Main results

Thirteen new studies were identified for the update of this review. In total, we included 33 cohort studies including 7876 participants investigating hepatic late adverse effects after antineoplastic treatment (especially chemotherapy and radiotherapy) for different types of childhood cancer, both haematological and solid malignancies. All studies had methodological limitations. The prevalence of hepatic late adverse effects, all defined in a biochemical way, varied widely, between 0% and 84.2%. Selecting studies where the outcome of hepatic late adverse effects was well-defined as alanine aminotransferase (ALT) above the upper limit of normal, indicating cellular liver injury, resulted in eight studies. In this subgroup, the prevalence of hepatic late adverse effects ranged from 5.8% to 52.8%, with median follow-up durations varying from three to 23 years since cancer diagnosis in studies that reported the median follow-up duration. A more stringent selection process using the outcome definition of ALT as above twice the upper limit of normal, resulted in five studies, with a prevalence ranging from 0.9% to 44.8%. One study investigated biliary tract injury, defined as gamma-glutamyltransferase (γGT) above the upper limit of normal and above twice the upper limit of normal and reported a prevalence of 5.3% and 0.9%, respectively. Three studies investigated disturbance in biliary function, defined as bilirubin above the upper limit of normal and reported prevalences ranging from 0% to 8.7%. Two studies showed that treatment with radiotherapy involving the liver (especially after a high percentage of the liver irradiated), higher BMI, and longer follow-up time or older age at evaluation increased the risk of cellular liver injury in multivariable analyses. In addition, there was some suggestion that busulfan, thioguanine, hepatic surgery, chronic viral hepatitis C, metabolic syndrome, use of statins, non-Hispanic white ethnicity, and higher alcohol intake (> 14 units per week) increase the risk of cellular liver injury in multivariable analyses. Chronic viral hepatitis was shown to increase the risk of cellular liver injury in six univariable analyses as well. Moreover, one study showed that treatment with radiotherapy involving the liver, higher BMI, higher alcohol intake (> 14 units per week), longer follow-up time, and older age at cancer diagnosis increased the risk of biliary tract injury in a multivariable analysis.

Authors' conclusions

The prevalence of hepatic late adverse effects among studies with an adequate outcome definition varied considerably from 1% to 53%. Evidence suggests that radiotherapy involving the liver, higher BMI, chronic viral hepatitis and longer follow-up time or older age at follow-up increase the risk of hepatic late adverse effects. In addition, there may be a suggestion that busulfan, thioguanine, hepatic surgery, higher alcohol intake (>14 units per week), metabolic syndrome, use of statins, non-Hispanic white ethnicity, and older age at cancer diagnosis increase the risk of hepatic late adverse effects. High-quality studies are needed to evaluate the effects of different therapy doses, time trends, and associated risk factors after antineoplastic treatment for childhood cancer.

PLAIN LANGUAGE SUMMARY

Adverse effects on the liver after treatment for childhood cancer

Review question

We reviewed the evidence for the effects of treatment for childhood cancer on the risk of adverse effects on the liver.

Background

Advances in the treatment of childhood cancer over the last decades have greatly improved the survival rates. Unfortunately, the improved prognosis has been accompanied by the occurrence of late, treatment-related complications. One of the adverse effects that can occur due to treatment of childhood cancer is damage to the liver. Liver adverse effects are common both during and soon after treatment. However, the evidence on adverse effects on the liver many years after treatment is still inconclusive. Adverse effect on the liver as a result of childhood cancer treatment is most often subclinical (asymptomatic). If liver disease becomes symptomatic, a person's complaints may include fatigue, jaundice, nausea, weight loss, and abdominal pain. The development of future treatment and follow-up policies should be based on high-quality evidence on the risk of, and associated risk factors for, adverse effects on the liver.

Study characteristics

The evidence is current to January 2018.

We found 33 cohort studies examining liver adverse effects after treatment for childhood cancer. There were 7876 cancer patients included that were treated for different types of childhood cancer, especially with chemotherapy, radiotherapy, and bone marrow transplantation.

The average follow-up duration in the studies that reported this varied from two years after the end of treatment to 25 years since primary cancer diagnosis.

Key results

We found that 1% to 53% of the childhood cancer survivors developed adverse effects on the liver after cancer treatment, measured by liver enzymes in the blood. Radiotherapy to the liver increases the risk of liver late adverse effects. In addition, busulfan, thioguanine, or liver surgery may increase the risk as well. Also, survivors with chronic viral hepatitis, metabolic syndrome, higher body mass index, higher alcohol intake, statin use, non-Hispanic white ethnicity, longer time since cancer diagnosis, and older age at cancer diagnosis seemed to have an increased risk of liver adverse effects.

Quality of the evidence

All studies had problems related to the quality of the evidence.

BACKGROUND

Survival rates have greatly improved as a result of more effective treatments for childhood cancer. Today, most children diagnosed with cancer are expected to become long-term cancer survivors (Curry 2006). Five-year disease-free survival now reaches 80% in Europe (Gatta 2009). Unfortunately, the improved prognosis has been accompanied by the occurrence of late, treatment-related complications. In two large cohort studies of childhood cancer survivors, nearly 75% experienced one or more late adverse effects (Geenen 2007; Oeffinger 2006).

Liver complications are common during and soon after treatment for childhood cancer (Field 2008). However, among long-term childhood cancer survivors the prevalence of chronic liver disease, like fibrosis, cirrhosis and consequently an increased risk of decompensated cirrhosis, malignancies and liver failure, is largely unknown. It has been suggested that survivors of childhood cancer who received chemotherapy, particularly methotrexate, 6-mercaptopurine, 6-thioguanine, busulphan and dactinomycin; bone marrow transplantation (BMT); radiotherapy involving the liver, including total body irradiation (TBI); or hepatectomy ((partial) removal of the liver) are at risk for developing hepatic late adverse effects (Bresters 2008; Castellino 2010; Dawson 2005; King 2001). However, the evidence has been inconclusive.

The aetiology (set of causes) of chronic liver disease following treatment for childhood cancer is complex as often more than one aetiologic factor is present. In addition to cancer treatment, other causes of chronic liver disease have been suggested, such as chronic viral hepatitis, iron overload, and potentially sinusoidal obstruction syndrome (SOS, previously termed veno-occlusive disease (VOD)) and graft-versus-host disease (GVHD) (Locasciulli 1997; Rizzo 2006; Strasser 1999). Regarding chronic viral hepatitis, patients who were treated for childhood cancer before effective hepatitis C virus (HCV) donor screening was implemented are especially at risk for transfusion-acquired HCV infection. Childhood cancer survivors differ from other groups with chronic viral hepatitis in that they acquired the infection at a young age and were likely to have received immunosuppressive or hepatotoxic therapy (Fink 1993; Strickland 2000).

For better development of primary and secondary hepatic protective strategies in childhood cancer, more insight into the association between cancer treatment and hepatic late adverse effects is essential. Furthermore, for the follow-up of childhood cancer survivors, it is crucial to know the risk and associated risk factors so that patients at greatest risk can be identified and adequate follow-up protocols established to reduce the consequences of hepatic late adverse effects. With increased survival duration after cancer, survivors are at risk for second malignancies and normal diseases of aging which will require additional pharmacotherapy. This additional morbidity risk also underscores the need for understanding the state of liver health in the long-term survivor of a childhood cancer, as long-term impaired liver function may limit treatment of other late effects, like second malignancies.

This is an update of the first systematic review evaluating the state of evidence on hepatic late adverse effects after antineoplastic (acting against cancer) treatment for childhood cancer (Mulder 2011).

OBJECTIVES

To evaluate all the existing evidence on the association between antineoplastic treatment (that is chemotherapy, radiotherapy involving the liver, surgery involving the liver and BMT) for childhood cancer and hepatic late adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

All study designs except case reports, case series (that is, description of non-consecutive cases) and studies including fewer than 10 participants that examined the association between antineoplastic treatment for childhood cancer and hepatic late adverse effects.

Types of participants

Childhood cancer survivors, diagnosed between the age of 0 and 18 years, who were at least one year after the end of their cancer treatment. More than 50% of the study group should have been diagnosed with a malignant disease. More than 50% of the study group should have been diagnosed between the age of 0 and 18 years. In addition, more than 50% of the study group should have been off treatment for at least one year. Because the aim of this systematic review was to evaluate the risk of, and associated risk factors for, hepatic late adverse effects after antineoplastic treatment for childhood cancer, we excluded studies in which the study population consisted solely of childhood cancer survivors with chronic viral hepatitis. In this way, it was possible to reliably evaluate risk factors for hepatic late adverse effects after cancer treatment.

Types of interventions

Treatment with chemotherapy, radiotherapy involving the liver (including TBI), surgery involving the liver, or BMT. Liver transplantations were excluded.

Types of outcome measures

Hepatic late adverse effects measured by liver enzymes (that is, alanine aminotransferase (ALT), also known as glutamic pyruvic transaminase (SGPT) and aspartate aminotransferase (AST), also known as glutamic oxaloacetic transaminase (SGOT)) to investigate cellular liver injury, and gamma-glutamyltransferase (γGT)) and alkaline phosphatase (ALP) or bilirubin, to investigate disturbances in bile excretion and biliary tract injury. In addition, measures of liver synthetic function were included: coagulation times (prothrombin time (PTT) or activated partial thromboplastin time (APTT)), albumin, or liver histology. These clinically relevant outcome measures were selected as recommended by an expert in the field (BK). In this review, we used the cut-off limit for normal and abnormal liver enzyme values as specified by the authors of the original studies.

Search methods for identification of studies

Electronic searches

The following electronic databases were searched: the Cochrane Central Library of Controlled Trials (CENTRAL) (*The Cochrane Library* 2018, Issue 1), MEDLINE (PubMed) (from 1945 to 9 January

2018) and Embase (Ovid) (from 1980 to 9 January 2018). The sensitive search strategies used for CENTRAL, MEDLINE, and Embase are presented in Appendix 1, Appendix 2 and Appendix 3.

Searching other resources

The reference lists of all relevant articles and reviews were screened for additional references which were not registered in CENTRAL, MEDLINE or Embase. We also scanned the conference proceedings of the International Society of Paediatric Oncology (SIOP) (from 2005 to 2017) and American Society of Pediatric Hematology/Oncology (ASPHO) (from 2013 to 2018) electronically (see Appendix 4).

We did not impose language restrictions.

Data collection and analysis

Selection of studies

After performing the search strategy described previously, two review authors independently selected studies that met the inclusion criteria. Discrepancies between review authors were resolved by consensus. If this was impossible, we achieved final resolution using a third-party arbitrator. We obtained the full text of any study seemingly meeting the inclusion criteria on the grounds of the title or abstract, or both, for closer inspection. We clearly stated the details of our reasons for exclusion of any study considered for this review.

Data extraction and management

For the original version of the review, two review authors independently performed data extraction using standardised forms. For the update of the review, the data extraction was performed by one reviewer and checked by another reviewer. The following data were extracted: study design, original cohort, described study group, study group of interest, study group with liver function testing, control group (if applicable), patient characteristics (including age, gender, body mass index (BMI), tumour type, years of survival, acute liver disease, and hepatitis virus infection), cancer treatment (including chemotherapy, radiotherapy involving the liver, BMT, and hepatectomy), duration and completion of follow-up, hepatic late adverse effects (including method of detection, definition, and outcome measure) and risk factors. In case of disagreement, a third review author was consulted.

We defined cohort studies as studies in which a group of consecutive patients treated for childhood cancer was followed from a similar well-defined point in the course of the disease (x-year survivors). The described study group could be the entire original cohort of childhood cancer survivors or a subgroup of the original cohort, based on well-defined inclusion criteria.

The participants in the original cohort represented the whole group of childhood cancer survivors. The described study group encompassed the childhood cancer survivors from the original cohort included in the study. The study group of interest was the childhood cancer survivors within the original cohort who received treatment with a high potential for hepatic late adverse effects. Finally, the study group with liver function testing was the childhood cancer survivors who were assessed for hepatic late adverse effects as well.

Assessment of risk of bias in included studies

The assessment of risk of bias was based on earlier described checklists for observational studies according to Evidence-Based Medicine Criteria (Grimes 2002; Laupacis 1994). Two review authors independently undertook the assessment of risk of bias of the included studies, concerning the selection of the study group, the follow-up and outcome assessments, and the methods used for risk estimation. For evaluation of internal validity, we assessed the risk of selection bias, attrition bias, detection bias, and confounding that was present in the included studies. It included the following items: representativeness of the study group, completeness of the follow-up, blinding of the outcome assessors, and adjustment for important confounding factors. We only assessed the risk of confounding for studies that reported on risk factors. For evaluation of external validity, we assessed the risk of reporting bias, which included the following items: definition of the study group, reporting the length of follow-up, objectiveness of the outcome definition, and definition of the analyses. We only assessed the definition of the analyses for studies that reported on risk factors.The 'risk of bias' assessment criteria for observational studies are described in additional Table 1. Discrepancies between review authors were resolved by consensus. In case of doubt, a third review author was consulted.

Measures of treatment effect

Prevalence, cumulative incidence, mean difference, relative risk, odds ratio, attributable risk, and other associated outcomes.

Assessment of heterogeneity

Heterogeneity was assessed by visual inspection of the tables. If there was evidence of substantial heterogeneity ($I^2 > 50\%$) (Higgins 2011), this was reported.

Assessment of reporting biases

We planned to construct a funnel plot to graphically ascertain the existence of publication bias. A rule of thumb is that tests for funnel plot asymmetry are used only when there are at least 10 studies in the meta-analysis. In the event of fewer than 10 studies, the power of the test is too low to distinguish chance from real asymmetry (Higgins 2011). Given that none of the included studies in the current analysis were pooled, we could not construct funnel plots.

Data synthesis

Data were entered into RevMan (Review Manager 2014) and analysed according to the guidelines of the *Cochrane Handbook* (Higgins 2011). All results are presented with the corresponding 95% confidence interval (95% CI), as calculated by the Wilson method. As this was not possible in RevMan, we used the following tool: http://epitools.ausvet.com.au/content.php?page=CIProportion. Because pooling was not possible due to substantial heterogeneity, we provided descriptive results of these studies.

Sensitivity analysis

We did not perform sensitivity analyses since pooling was not possible for any of the outcomes. We did take into account the risk of bias in studies included in this systematic review in the interpretation of the results.

RESULTS

Description of studies

Results of the search

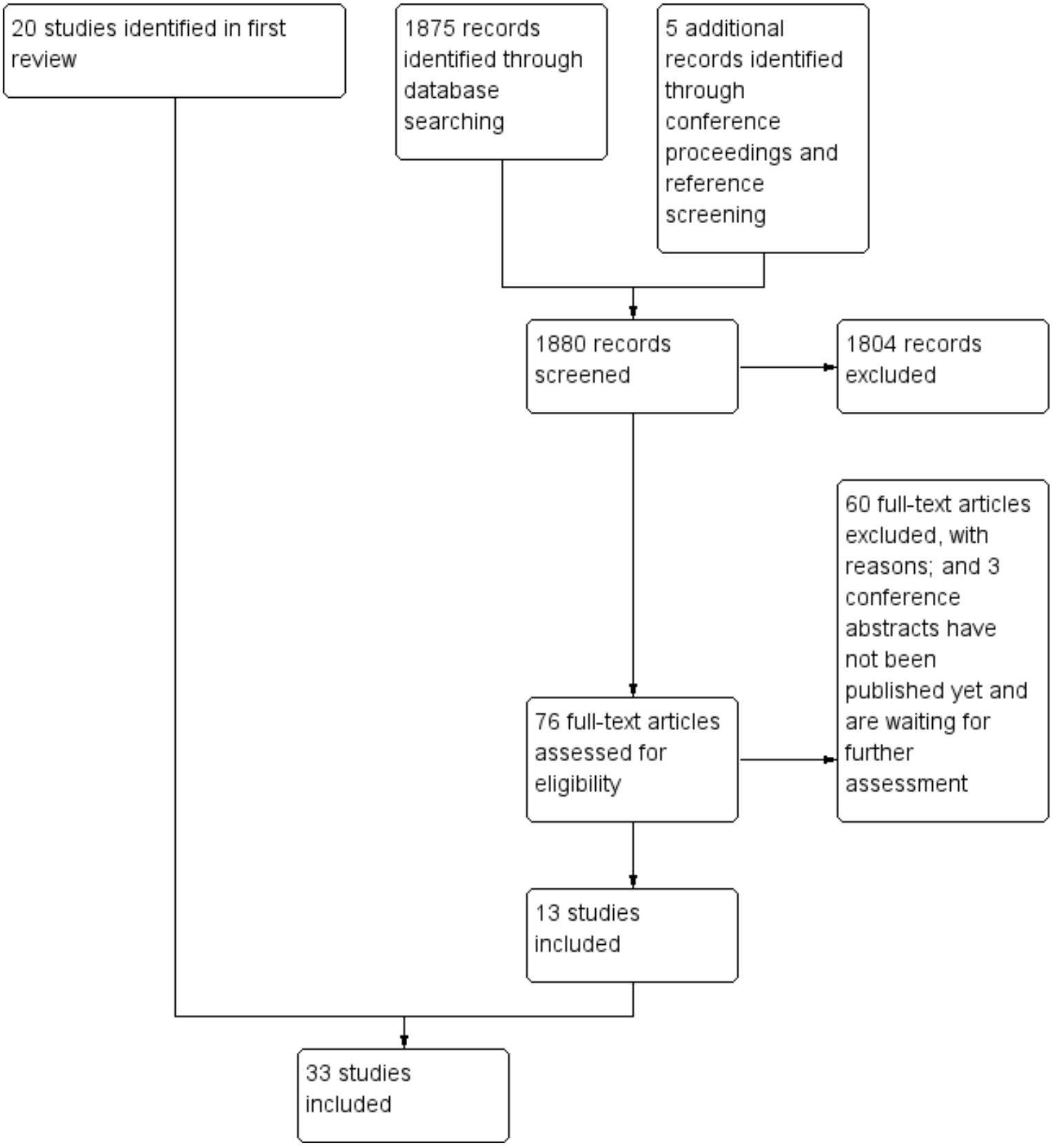
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

After performing the searches of the electronic databases of CENTRAL, MEDLINE (PubMed) and Embase (Ovid) (in June 2009), we identified 1703 references. Following initial screening of the titles and abstracts, or both, we excluded 1572 which clearly did not meet all prespecified criteria for this systematic review. We obtained 131 articles in full text, of which seven met all the inclusion criteria. For an Icelandic article, it was unclear if the study was eligible for inclusion. We are waiting for the translation. Therefore, this study was added to the Characteristics of studies awaiting classification table. The other 123 studies were not eligible for inclusion for the reasons described in the Characteristics of excluded studies table.

After scanning the reference lists of relevant studies and reviews, 55 additional articles were retrieved for more detailed examination, of which 13 met all the inclusion criteria. Forty-two studies were added to the Characteristics of excluded studies table. By scanning the conference proceedings of SIOP, we identified two eligible studies that have not been published yet and are waiting for further assessment (see the Characteristics of studies awaiting classification table).

Running the searches for the update in CENTRAL, MEDLINE and Embase (in January 2018) yielded a total of 1875 new references (see Figure 1). Following screening of the titles, abstracts, or both, we excluded 1804 which clearly did not meet the criteria for considering studies for this review. We obtained 71 articles in full text, of which 11 met all the inclusion criteria. In addition, the electronic search yielded one abstract of a conference proceeding. At the time of data extraction, this study was published and therefore included as well. The other 59 articles were excluded for reasons described in the Characteristics of excluded studies table. Scanning the reference lists of relevant studies and reviews, two articles were retrieved for detailed examination. One study met the inclusion criteria and one study did not meet the inclusion criteria and was added to the Characteristics of excluded studies table. By scanning the conference proceedings of SIOP and ASPHO, we identified three eligible studies that have not been published yet and are waiting for further assessment (see the Characteristics of studies awaiting classification table).

Figure 1. Study flow diagram.



Included studies

In total, our search identified 33 eligible studies examining the association between antineoplastic treatment for childhood cancer and hepatic late adverse effects. Characteristics of the included studies are summarised below and their baseline characteristics are described in the Characteristics of included studies table. It should be noted, however, that there might be partial overlap in included participants between the following studies: Locasciulli 1983, Locasciulli 1985, Locasciulli 1991a and Locasciulli 1997a; Guido 1991 and Rossetti 1991; Hyodo 2012 and Tomita 2011.

The total number of participants included in the 33 identified cohort studies who received treatment with a high potential for hepatic late adverse effects was 7876, ranging from 19 to 2753 childhood cancer survivors per study. Sixteen studies included participants diagnosed with leukaemia (that is, acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), and acute non-lymphoblastic leukaemia (ANLL)) (Aricò 1994; Bessho 1994; Chotsampancharoen 2009; Delvecchio 2017; El-Rashedy 2017; Guido 1991; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Locasciulli 1997a; Matsuzaki 2001; Ratner 1986; Rossetti 1991; Skou 2014; Vora 2006; Weber 1987); four studies included participants with various forms of leukaemia and non-malignant disease (Frisk 1998; Hyodo 2012; Locasciulli 1997a; Tomita 2011); one study with Wilms' tumour, neuroblastoma and hepatoblastoma (Tefft 1970); one study with hepatoblastoma (Stringer 1995); one study with various forms of leukaemia, benign haematological diseases, immunological diseases, and other inborn errors (Bresters 2008); one study with Wilms' tumour (Jagt 2009); one study with neuroblastoma (French 2012); and eight studies with various tumours (Ballauff 1999; Green 2019; Gunn 2016; Hudson 2013; Landier 2012; Mulder 2013; Schempp 2016; Seth 2017).

In 31 of the 33 studies, participants were treated with chemotherapy; in two studies, it was unclear whether the participants received chemotherapy (Chotsampancharoen 2009; Schempp 2016). In 24 studies, the type of chemotherapy was mentioned, which varied considerably across the studies (Bessho 1994; Bresters 2008; Delvecchio 2017; El-Rashedy 2017; Frisk 1998; Green 2019; Guido 1991; Hudson 2013; Hyodo 2012; Jagt 2009; Landier 2012; Locasciulli 1983; Locasciulli 1985; Locasciulli 1997b; Matsuzaki 2001; Mulder 2013; Ratner 1986; Rossetti 1991; Skou 2014; Stringer 1995; Tefft 1970; Tomita 2011; Vora 2006; Weber 1987). Nine studies mentioned the chemotherapy dose according to the treatment protocol, which varied widely (Bessho 1994; Hudson 2013; Jagt 2009; Landier 2012; Locasciulli 1997b; Matsuzaki 2001; Stringer 1995; Vora 2006; Weber 1987). Four studies reported the dose actually received by the participants (Bessho 1994; Hudson 2013; Landier 2012; Skou 2014). Eighteen of the 33 studies reported whether the participants were treated with radiotherapy involving the liver (Bresters 2008; Chotsampancharoen 2009; Delvecchio 2017; El-Rashedy 2017; French 2012; Frisk 1998; Green 2019; Gunn 2016; Hudson 2013; Hyodo 2012; Landier 2012; Locasciulli 1997b; Matsuzaki 2001; Mulder 2013; Skou 2014; Stringer 1995; Tefft 1970; Tomita 2011), of which fourteen studies included participants who received radiotherapy involving the liver (Bresters 2008; Chotsampancharoen 2009; French 2012; Frisk 1998; Green 2019; Gunn 2016; Hudson 2013; Hyodo 2012; Landier 2012; Locasciulli 1997b; Mulder 2013; Stringer 1995; Tefft 1970; Tomita 2011). Fourteen studies mentioned the radiotherapy field and dose, which varied from 5.0 to 14.4 Gy TBI (Chotsampancharoen 2009; French 2012; Frisk 1998; Hyodo 2012; Locasciulli 1997b; Mulder 2013; Tomita 2011); 3.0 to 76.0 Gy (thoraco-)abdominal irradiation (French 2012; Hudson 2013; Hyodo 2012; Landier 2012; Mulder 2013; Tomita 2011); and less than 25 Gy to more than 35 Gy liver irradiation (Tefft 1970). One study calculated the volumetric dose to the liver and reported that the median percentage of liver that received 10 Gy was 51.4%, the median percentage of liver that received 15 Gy was 34.6% and the median percentage of liver that received 20 Gy was 25.3% (Green 2019). Four studies included participants treated with a hepatectomy (Green 2019; Mulder 2013; Stringer 1995; Tefft 1970). Moreover, fifteen studies included participants treated with BMT (Bresters 2008; Chotsampancharoen 2009; French 2012; Frisk 1998; Green 2019; Gunn 2016; Hudson 2013; Hyodo 2012; Landier 2012; Locasciulli 1991a; Locasciulli 1997b; Mulder 2013; Schempp 2016; Skou 2014; Tomita 2011).

Twenty-four studies mentioned the age at diagnosis. Within studies reporting mean or median values, the mean/median age ranged from 0.2 to 10.2 years (Bessho 1994; Delvecchio 2017; El-Rashedy 2017; French 2012; Green 2019; Guido 1991; Gunn 2016; Hudson 2013; Hyodo 2012; Jagt 2009; Landier 2012; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Locasciulli 1997a; Mulder 2013; Schempp 2016; Seth 2017; Skou 2014; Stringer 1995; Tefft 1970; Tomita 2011; Vora 2006; Weber 1987). The age at follow-up was reported by seventeen studies (Aricò 1994; Ballauff 1999; Bessho 1994; Delvecchio 2017; El-Rashedy 2017; French 2012; Green 2019; Gunn 2016; Hudson 2013; Hyodo 2012; Landier 2012; Mulder 2013; Rossetti 1991; Schempp 2016; Seth 2017; Skou 2014; Tomita 2011) and ranged from a mean/median 9.7 to 32.0 years in studies that reported mean or median values. All but four studies (Gunn 2016; Ratner 1986; French 2012; Vora 2006) mentioned the gender of the included participants. The percentage of females in these studies varied between 0% and 64%. For the 31 studies that reported follow-up duration, the reported mean or median duration varied widely from 2.0 years after the end of treatment to 25.1 years since primary cancer diagnosis (Aricò 1994; Ballauff 1999; Bessho 1994; Bresters 2008; Chotsampancharoen 2009; Delvecchio 2017; El-Rashedy 2017; French 2012; Frisk 1998; Green 2019; Guido 1991; Gunn 2016; Hudson 2013; Hyodo 2012; Landier 2012; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b; Mulder 2013; Ratner 1986; Rossetti 1991; Schempp 2016; Seth 2017; Stringer 1995; Skou 2014; Tefft 1970; Tomita 2011; Vora 2006; Weber 1987).

In the included studies, hepatic late adverse effects were variably defined using ALT, AST, γGT, ALP, bilirubin, and PTT. Fourteen studies defined hepatic late adverse effects by abnormal values of serum ALT or AST, or both (Aricò 1994; Bessho 1994; Bresters 2008; Guido 1991; Gunn 2016; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b; Matsuzaki 2001; Ratner 1986; Rossetti 1991; Vora 2006); eight studies defined hepatic late adverse effects by describing separate abnormal values of ALT, AST ALP, bilirubin prothrombin ratio or albumin (Chotsampancharoen 2009; Delvecchio 2017; El-Rashedy 2017; French 2012; Green 2019; Landier 2012; Mulder 2013; Skou 2014); nine studies defined hepatic late adverse effects by combined measurements of ALT, AST, bilirubin, γGT, ALP and/or PTT (Ballauff 1999; Frisk 1998; Hudson 2013; Hyodo 2012; Jagt 2009; Schempp 2016; Tefft 1970; Tomita 2011; Weber 1987); and for two studies, it was unclear which biochemical liver function tests were used (Seth 2017; Stringer 1995). In 19 studies, the upper limits of normal were described

(Aricò 1994; Ballauff 1999; Bessho 1994; Bresters 2008; French 2012; Green 2019; Hudson 2013; Jagt 2009; Landier 2012; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b; Mulder 2013; Ratner 1986; Rossetti 1991; Skou 2014; Weber 1987). Ten studies defined hepatic late adverse effects as ALT and/or AST above the upper limit of normal (Aricò 1994; Bessho 1994; Bresters 2008; French 2012; Green 2019; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b; Mulder 2013; Skou 2014); five studies as ALT and/or AST above two times the upper limit of normal (Bresters 2008; Landier 2012; Mulder 2013; Ratner 1986; Rossetti 1991); two studies as ALT or AST, or both, above three times the upper limit of normal (Locasciulli 1983; Locasciulli 1985); two studies as ALP above the upper limit of normal (French 2012; Skou 2014); three studies as bilirubin above the upper limit of normal (French 2012; Landier 2012; Skou 2014); one study as γGT above and two times above the upper limit of normal (Mulder 2013); and four studies as combinations of ALT, AST, bilirubin, γGT and/or ALP above the upper limit of normal (Ballauff 1999; Hudson 2013; Jagt 2009; Landier 2012; Weber 1987). In four studies, liver biopsies were performed in a selected group of participants (Locasciulli 1997a; Ratner 1986; Tomita 2011; Vora 2006).

Risk of bias in included studies

Data on the risk of bias in the 33 cohort studies are described in the Characteristics of included studies table and are shown in Figure 2 and Figure 3. All studies were found to have methodological limitations.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

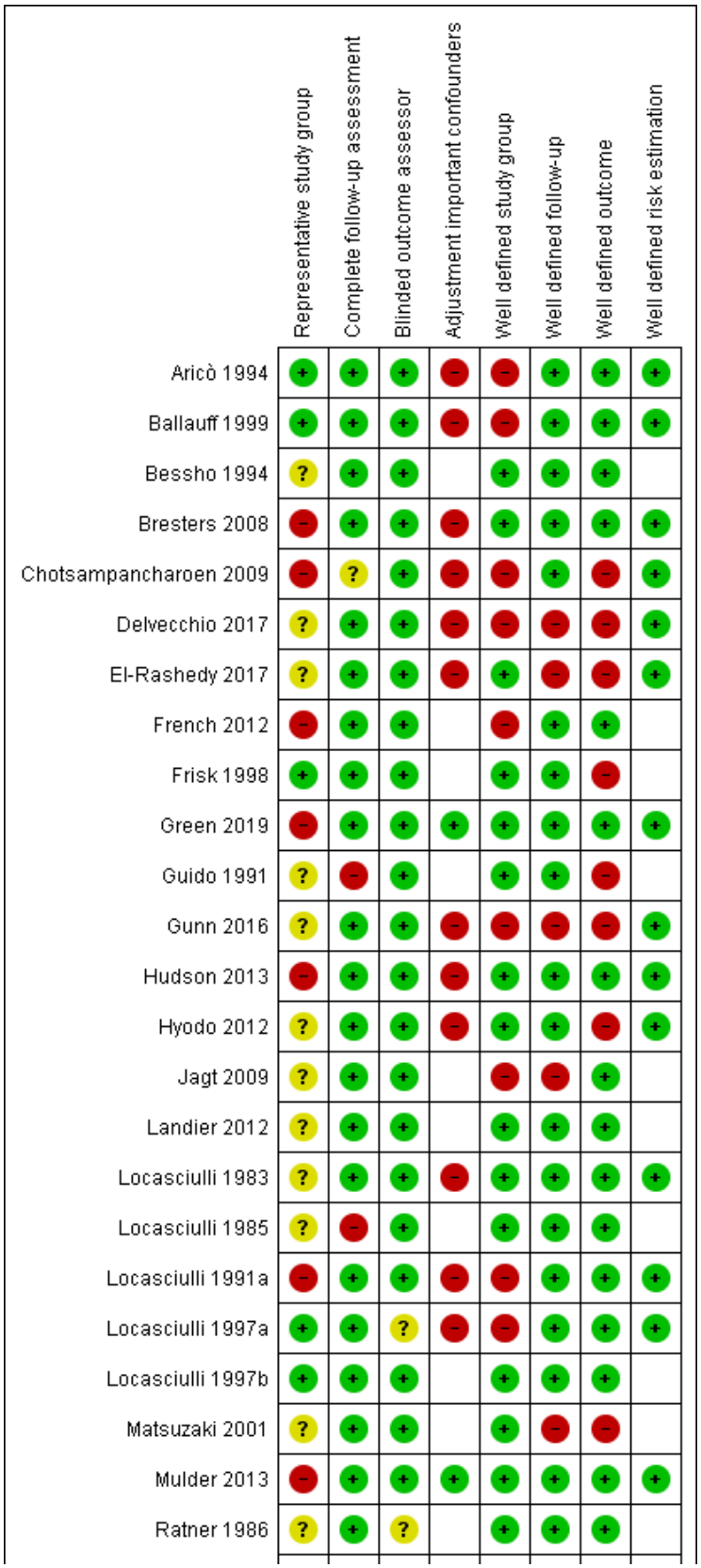


Figure 2. (Continued)

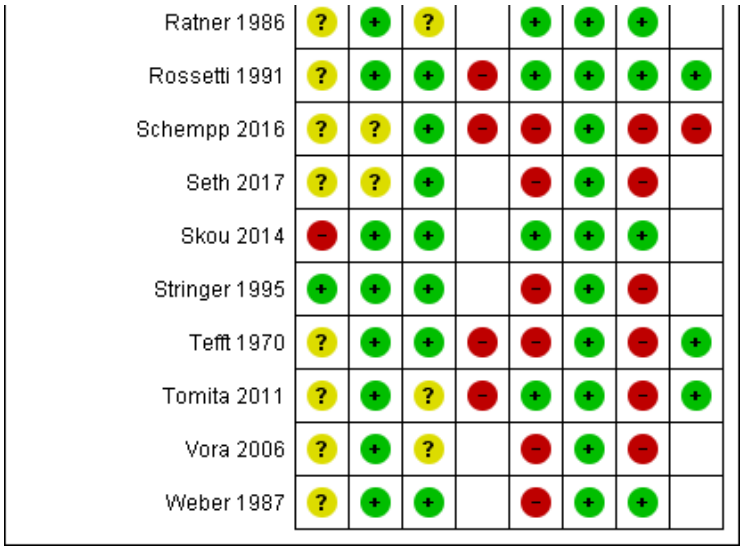
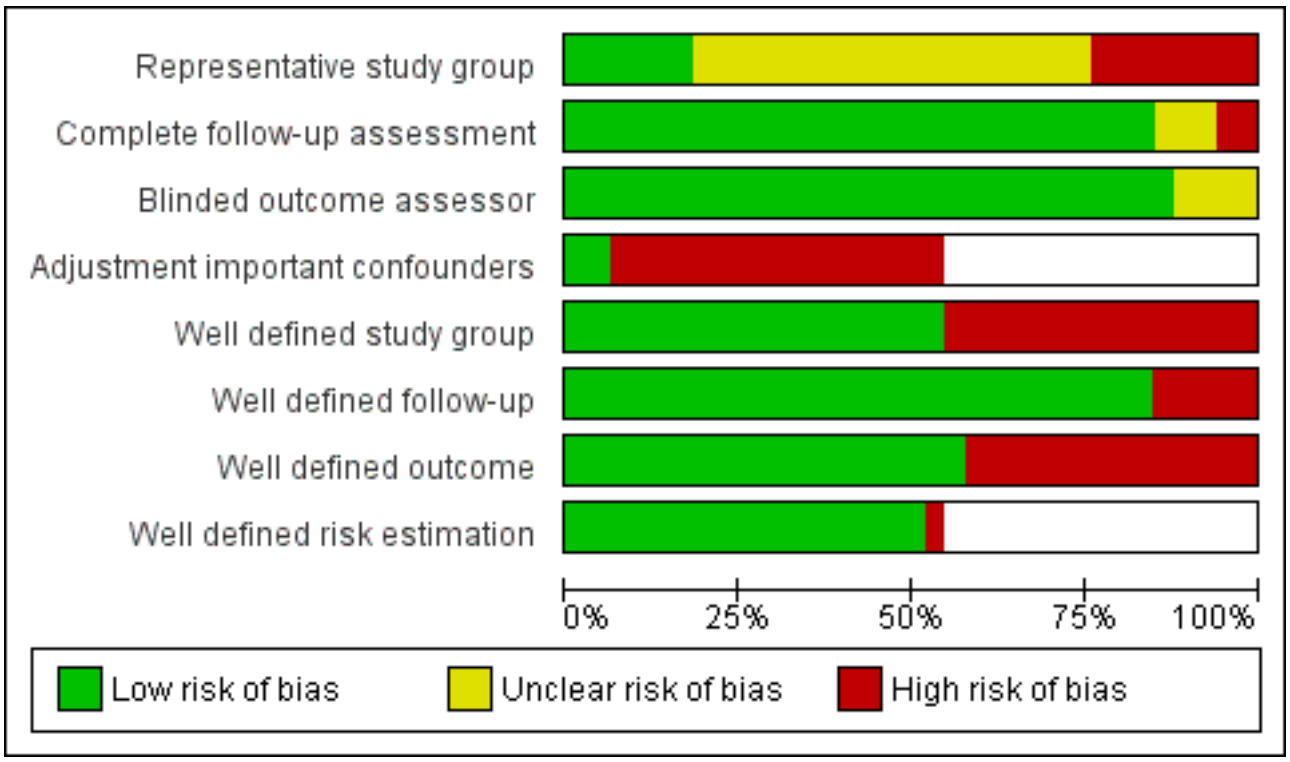


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



For evaluation of internal validity, we assessed the risk of selection bias, attrition bias, detection bias, and confounding present in the included studies.

In five of the 33 studies, the described study group consisted of the entire original cohort of childhood cancer survivors (Aricò 1994; Ballauff 1999; Frisk 1998; Locasciulli 1997b; Stringer 1995). Nine studies described a subgroup of the original cohort (Bresters 2008; Chotsampancharoen 2009; French 2012; Green 2019; Hudson 2013; Locasciulli 1991a; Locasciulli 1997a; Mulder 2013; Skou 2014). In one study, this subgroup consisted of more than 90% of the original cohort (Locasciulli 1997a). In the other eight studies, this subgroup neither consisted of more than 90% of the original cohort nor was it a random sample with respect to the cancer treatment (Bresters 2008; Chotsampancharoen 2009; French 2012; Green 2019; Hudson 2013; Locasciulli 1991a; Mulder 2013; Skou 2014). For 19 studies, the number of participants in the original cohort was not mentioned (Bessho 1994; Delvecchio 2017; El-Rashedy

2017; Guido 1991; Gunn 2016; Hyodo 2012; Jagt 2009; Landier 2012; Locasciulli 1983; Locasciulli 1985; Matsuzaki 2001; Ratner 1986; Rossetti 1991; Schempp 2016; Seth 2017; Tefft 1970; Tomita 2011; Vora 2006; Weber 1987). For these studies, it was unclear whether the described study group consisted of more than 90% of the original cohort of childhood cancer survivors or whether it was a random sample with respect to the cancer treatment. Hence, in six of the 33 studies (18.2%) the study group was representative. So, selection bias could not be ruled out in 81.8% of the included studies.

Twenty-eight studies (84.8%) had an adequate follow-up (based on > 60% of the study group of interest) (Aricò 1994; Ballauff 1999; Bessho 1994; Bresters 2008; Delvecchio 2017; El-Rashedy 2017; French 2012; Frisk 1998; Green 2019; Gunn 2016; Hudson 2013; Hyodo 2012; Jagt 2009; Landier 2012; Locasciulli 1983; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b; Matsuzaki 2001; Mulder 2013; Ratner 1986; Rossetti 1991; Skou 2014; Stringer 1995; Tefft 1970; Tomita 2011; Vora 2006; Weber 1987), of which 22 studies assessed the outcome for more than 90% of the study group of interest (Aricò 1994; Ballauff 1999; Bessho 1994; Bresters 2008; Delvecchio 2017; El-Rashedy 2017; Frisk 1998; Green 2019; Gunn 2016; Hudson 2013; Hyodo 2012; Landier 2012; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b; Mulder 2013; Ratner 1986; Skou 2014; Stringer 1995; Tomita 2011; Vora 2006; Weber 1987). Two studies assessed the outcome for less than 60% of the study group of interest and thus were scored as having incomplete follow-up (Guido 1991; Locasciulli 1985), and, for three studies, the completion of follow-up was unclear (Chotsampancharoen 2009; Schempp 2016; Schempp 2016). Hence, there was a risk of attrition bias in five of the 33 studies (15.2%)

In all studies, liver enzymes were biochemically measured. This outcome is not likely to be influenced by lack of blinding. In four studies that performed liver biopsies, it was unclear if the outcome assessors were blinded (Locasciulli 1997a; Ratner 1986; Tomita 2011; Vora 2006).

Eighteen studies assessed possible risk factors for the development of hepatic late adverse effects (Aricò 1994; Ballauff 1999; Bresters 2008; Chotsampancharoen 2009; Delvecchio 2017; El-Rashedy 2017; Green 2019; Gunn 2016; Hudson 2013; Hyodo 2012; Locasciulli 1983; Locasciulli 1991a; Locasciulli 1997a; Mulder 2013; Rossetti 1991; Schempp 2016; Tefft 1970; Tomita 2011). Only two out of these 18 studies (Green 2019; Mulder 2013) conducted multivariable analyses with adjustment for important confounders. So, there was a risk of confounding in 88.9% of the studies which assessed possible risk factors.

For evaluation of external validity, we assessed the risk of reporting bias present in the included studies.

In 18 of the 33 studies (54.5%), the study group was well-defined in terms of antineoplastic therapy exposure and chronic viral hepatitis (Bessho 1994; Bresters 2008;El-Rashedy 2017; Green 2019; Frisk 1998; Guido 1991; Hudson 2013; Hyodo 2012; Landier 2012; Locasciulli 1983; Locasciulli 1985; Locasciulli 1997b; Matsuzaki 2001; Mulder 2013; Skou 2014; Ratner 1986; Rossetti 1991; Tomita 2011). The other 15 studies failed to mention the type of chemotherapy (Aricò 1994; Ballauff 1999; French 2012; Gunn 2016; Locasciulli 1991a; Locasciulli 1997a; Schempp 2016; Seth 2017) or the number of participants with chronic viral hepatitis (Chotsampancharoen 2009; Delvecchio 2017; Gunn 2016; Jagt 2009; Schempp 2016; Stringer 1995; Tefft 1970; Vora 2006; Weber 1987).

Twenty-eight studies (84.8%) reported the length of follow-up and therefore had a well-defined follow-up (Aricò 1994; Ballauff 1999; Bessho 1994; Bresters 2008; Chotsampancharoen 2009; French 2012; Frisk 1998; Green 2019; Guido 1991; Hudson 2013; Hyodo 2012; Landier 2012; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b; Mulder 2013; Ratner 1986; Rossetti 1991; Schempp 2016; Seth 2017; Skou 2014; Stringer 1995; Tefft 1970; Tomita 2011; Vora 2006; Weber 1987).

In 19 studies, the upper limits of normal for the liver function tests that were used were described (Aricò 1994; Ballauff 1999; Bessho 1994; Bresters 2008; French 2012; Green 2019; Hudson 2013; Jagt 2009; Landier 2012; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b; Mulder 2013; Skou 2014; Ratner 1986; Rossetti 1991; Weber 1987). The other studies did not mention the upper limits of normal. So 19 of the 33 studies (57.6%) had a well-defined outcome.

Eighteen studies assessed possible risk factors for the development of hepatic late adverse effects, of which all but one had a well-defined risk estimation (94.4%) (Aricò 1994; Ballauff 1999; Bresters 2008; Chotsampancharoen 2009; Delvecchio 2017; El-Rashedy 2017; Green 2019; Gunn 2016; Hudson 2013; Hyodo 2012; Locasciulli 1983; Locasciulli 1991a; Locasciulli 1997a; Mulder 2013; Rossetti 1991; Tefft 1970; Tomita 2011).

Hence, reporting bias could not be ruled out in up to 63.6% of the included studies.

Effects of interventions

Prevalence of hepatic late adverse effects

The prevalence of hepatic late adverse effects as measured by liver enzymes, bilirubin, or coagulation times was reported in all but three studies (Chotsampancharoen 2009; Delvecchio 2017; El-Rashedy 2017) and varied widely between 0% and 84.2% (see Characteristics of included studies). However, five studies estimated the prevalence of hepatic late adverse effects in a selected group of participants who were diagnosed with abnormal liver function during or soon after the cancer treatment (Guido 1991; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Vora 2006). Excluding these studies resulted in a reported prevalence of 0% to 58.0%.

Furthermore, hepatic late adverse effects were defined using different liver function tests with varying cut-off limits. When selecting studies with a well-defined outcome, that is, if the upper limits of normal for the liver function tests were described in the definition of hepatic late adverse effects, 19 studies remained (Aricò 1994; Ballauff 1999; Bessho 1994; Bresters 2008; French 2012; Green 2019; Hudson 2013; Jagt 2009; Landier 2012; Locasciulli 1983; Locasciulli 1985; Locasciulli 1991a; Locasciulli 1997a; Locasciulli 1997b; Mulder 2013; Ratner 1986; Rossetti 1991; Skou 2014; Weber 1987).

Cellular liver injury: ALT and AST

Eight studies defined hepatic late adverse effects as ALT above the upper limit of normal with prevalences ranging from 5.8% to 52.8% (Aricò 1994; Bessho 1994; French 2012; Green 2019; Locasciulli 1997a; Locasciulli 1997b; Mulder 2013; Skou 2014) (Table 2). Two

studies defined hepatic late adverse effects as AST above the upper limit of normal with a prevalence of 1.1% and 13.0%, respectively (Skou 2014; French 2012) (Table 3). One study defined hepatic late adverse effects as ALT or AST above the upper limit of normal with a prevalence of 24.5% (Bresters 2008) (Table 4). Because unexplained heterogeneity was detected by visual inspection of the tables, we were not able to pool the results of the studies. The cancer treatment varied across the studies. In all studies, the included participants were treated with chemotherapy. The chemotherapy regimens varied considerably. In five studies, it was reported that participants were also treated with TBI and BMT (Bresters 2008; French 2012; Green 2019; Locasciulli 1997b; Mulder 2013), but this could not explain the variation in the prevalence (5.8% to 52.8%). Selecting studies in which a considerable proportion of the participants had a chronic viral hepatitis resulted in three studies with a prevalence of elevated ALT ranging from 21.6% to 52.8% (Aricò 1994; Locasciulli 1997a; Locasciulli 1997b). Although other potential sources of heterogeneity (that is, risk of bias present in the studies, age at diagnosis, follow-up duration, gender, acute liver morbidity) also varied across these studies, they could not explain the variation in the prevalence of hepatic late adverse effects.

Four studies defined hepatic late adverse effects as ALT above two times the upper limit of normal (Landier 2012; Mulder 2013; Ratner 1986; Rossetti 1991). The prevalence ranged from 0.9% to 44.8% (Table 5). Heterogeneity was also detected in these figures. Chronic viral hepatitis could partly explain the variation in the prevalence reported in Rossetti 1991 (44.8%), Ratner 1986 (23.1%), Landier 2012 (2.3%) and Mulder 2013 (0.9%), with infection rates of 62.5% (HBV), 12.8% (HBV), 8.9% (HCV), and 0% respectively. There were no differences in the risk of bias present in these studies. Although other potential sources of heterogeneity (age at diagnosis, follow-up duration, gender, acute liver morbidity) also varied across these studies, they could not explain the variation in the prevalence of hepatic late adverse effects.

In addition, one study defined hepatic late adverse effects as AST above two times the upper limit of normal with a prevalence of 2.3% (Landier 2012) (Table 6). Two studies defined hepatic late adverse effects as ALT or AST two times above the upper limit of normal with a prevalence of 7.9% and 2.7%, respectively (Bresters 2008; Landier 2012) (Table 7).

Billiary tract injury: γGT and ALP

One study investigated biliary tract injury defined as γGT above and twice above the upper limit of normal and reported a prevalence of 5.3% and 0.9%, respectively (Mulder 2013) (Table 8 and Table 9). Two studies investigated biliary tract injury defined as ALP above the upper limit of normal, with prevalences of 4.3% and 11.1% respectively (French 2012; Skou 2014) (Table 10).

Disturbance in biliary function: bilirubin

Three studies defined hepatic late adverse effects as bilirubin above the upper limit of normal. Prevalences ranged from 8.7% abnormal unconjugated bilirubin, 0% abnormal conjugated bilirubin (French 2012), 1.1% abnormal total bilirubin (Landier 2012) and 1.0% abnormal bilirubin (Skou 2014) (Table 11).

Because hepatic late adverse effects in the studies of Ballauff 1999, Hudson 2013, Jagt 2009 and Weber 1987 were defined using different assessment methods, we were not able to combine the results of these four studies.

In four studies, liver biopsies were performed to evaluate hepatic late adverse effects in two, three, four, and ten participants, respectively (Locasciulli 1997a; Ratner 1986; Tomita 2011; Vora 2006). All liver biopsies were performed on clinical indication: persistent high ALT levels (Locasciulli 1997a), chronic HBV infection (Ratner 1986), fatty liver (Tomita 2011), and splenomegaly during and soon after chemotherapy (Vora 2006). Participants were diagnosed with either chronic persistent hepatitis, chronic lobular hepatitis, cirrhosis, portal fibrosis, nodular regenerative hyperplasia, or fatty liver.

Risk factors for hepatic late adverse effects

Eighteen studies investigated possible risk factors for hepatic late adverse effects (Aricò 1994; Ballauff 1999; Bresters 2008; Chotsampancharoen 2009; Delvecchio 2017; El-Rashedy 2017; Green 2019; Gunn 2016; Hudson 2013; Hyodo 2012; Locasciulli 1983; Locasciulli 1991a; Locasciulli 1997a; Mulder 2013; Rossetti 1991; Schempp 2016; Tefft 1970; Tomita 2011). However, only two studies (Green 2019; Mulder 2013) conducted multivariable analyses. Radiotherapy involving the liver, methotrexate, mercaptopurine, thioguanine, dactinomycin, busulphan, other antimetabolites, other cytotoxic antibiotics, other alkylating agents, plant alkaloids, other chemotherapeutic agents, liver resection, BMI, alcohol intake, chronic viral hepatitis C, age at primary cancer diagnosis, age at evaluation, follow-up time since primary cancer diagnosis, gender, metabolic syndrome, statins, and ethnicity were evaluated as possible risk factors for hepatic late adverse effects in these two studies.

Chronic viral hepatitis (HCV, HBV, HBV-HDV co-infection (Aricò 1994; Ballauff 1999; Locasciulli 1983; Locasciulli 1991a; Locasciulli 1997a; Rossetti 1991)), cancer treatment (cyclophosphamide with TBI or TAI, cyclophosphamide with busulphan, other (Bresters 2008); mercaptopurine, thioguanine, and/or radiotherapy involving the liver (Hudson 2013); cranial radiotherapy (CRT) (Gunn 2016); CRT with TBI, TBI, TAI with chemotherapy (Tomita 2011); higher radiotherapy dose, radiotherapy field (right lobe, left lobe, entire liver, remaining liver) (Tefft 1970); standard versus low-dose asparaginase (El-Rashedy 2017)), older age at haematopoietic stem cell transplantation (HSCT), diagnosis of a benign haematological disease, gender, HSCT donor type (matched sibling donor, other), stem cell source, early post-transplant morbidity (viral reactivation, SOS, acute GVHD) (Bresters 2008), overweight (Gunn 2016), iron overload (Chotsampancharoen 2009; El-Rashedy 2017; Schempp 2016), and fatty liver (Hyodo 2012; Delvecchio 2017) were investigated as possible risk factors for hepatic late adverse effects in univariable analyses.

Evidence suggests that treatment with radiotherapy involving the liver (especially after a higher percentage of the liver irradiated), higher BMI, and longer follow-up time or older age at evaluation increase the risk of cellular liver injury in multivariable analyses (Green 2019; Mulder 2013). In addition, some evidence suggests that busulfan, thioguanine, hepatic surgery, higher alcohol intake (> 14 units per week), chronic viral hepatitis C, metabolic syndrome, use of statins, and non-Hispanic white ethnicity increase the risk of cellular liver injury in multivariable analyses (Green 2019; Mulder 2013). Chronic viral hepatitis was shown to increase the risk of cellular liver injury in six univariable analyses as well (Aricò 1994; Ballauff 1999; Locasciulli 1983; Locasciulli 1991a; Locasciulli 1997a; Rossetti 1991). Moreover, there is some suggestion that treatment with radiotherapy involving the liver, higher BMI, higher alcohol

intake (> 14 units per week), longer follow-up time and older age at cancer diagnosis increase the risk of biliary tract injury in multivariable analyses (Mulder 2013).

The identification of other risk factors has not been universally identified across all studies (see Characteristics of included studies, and additional Table 12 and Table 13).

DISCUSSION

In this update of the first systematic review, all available evidence on the association and risk of hepatic late adverse effects after treatment for childhood cancer was critically evaluated among 33 studies that met the inclusion criteria. The reported prevalence of hepatic late adverse effects varied considerably, between 0% and 84.2%. Part of this wide range could be explained by the variation in outcome definition. Selecting studies where the outcome of hepatic late adverse effects was well-defined as ALT above the upper limit of normal, indicating cellular liver injury, resulted in eight studies. In this subgroup, the prevalence of hepatic late adverse effects ranged from 5.8% to 52.8%. A more stringent selection using an outcome definition of ALT above twice the upper limit of normal resulted in four studies, with a prevalence ranging from 0.9% to 44.8%. There is some suggestion that chronic viral hepatitis could explain a part of this variation. One study investigated biliary tract injury defined as γGT above the upper limit of normal and above twice the upper limit of normal and reported a prevalence of 5.3% and 0.9%, respectively. Three studies investigated disturbances in biliary function defined as bilirubin above the upper limit of normal and reported prevalences ranging from 0% to 8.7%. Since only two studies evaluated risk factors by multivariable analysis, there is no strong evidence regarding which paediatric patients are at the greatest risk of developing hepatic late adverse effects. There is a suggestion that radiotherapy involving the liver, including a higher irradiated volume, higher BMI, chronic viral hepatitis, and longer follow-up time or older age at follow-up increase the risk of cellular liver injury. In addition, there is some suggestion that busulfan, thioguanine, hepatic surgery, higher alcohol intake (> 14 units per week), metabolic syndrome, use of statins, and non-Hispanic white ethnicity increase the risk of cellular liver injury. Moreover, there is some suggestion that treatment with radiotherapy involving the liver, higher BMI, higher alcohol intake (> 14 units per week), longer follow-up time and older age at cancer diagnosis increase the risk of biliary tract injury. The studies in this systematic review showed that even many years after cancer diagnosis (> 25 years), hepatic late adverse effects were still detected. Since none of the studies investigated the longitudinal development of hepatic late adverse effects many years after treatment, it is unclear if liver function recovers or deteriorates over time.

From previous research, it is known that methotrexate, 6-mercaptopurine, 6-thioguanine, busulphan, and dactinomycin increase the risk of liver toxicity during or soon after cancer treatment (Field 2008; King 2001). It has been speculative that these chemotherapeutics also increase the risk of hepatic late adverse effects. In the current systematic review, only two studies investigated the association between individual chemotherapeutic agents and hepatic late adverse effects. One study (Green 2019) found an association between elevated ALT levels and treatment with busulfan and thioguanine, but the other study did not find an association (Mulder 2013). There was a great diversity in antineoplastic treatment among the participants in the other individual studies, so it was impossible to compare the effects of specific chemotherapeutics from the included studies. Hence, despite the clear association between certain chemotherapeutic agents and acute transaminase elevation, sinusoidal obstruction syndrome (SOS) and synthetic liver dysfunction (Field 2008; King 2001), the evidence for an increased risk of hepatic late adverse effects after treatment with methotrexate, mercaptopurine, thioguanine, busulphan or dactinomycin is less clear.

Three included studies investigated the association between radiotherapy to the liver and hepatic late adverse effects (Green 2019; Mulder 2013; Tefft 1970). Green 2019 showed that radiotherapy involving the liver is an important risk factor for cellular liver injury and that volume plays an important role. They identified a significant association between the percentage of the liver treated with ≥ 10 Gy, ≥ 15 Gy, or ≥ 20 Gy and elevated ALT .Mulder 2013 showed that radiotherapy involving the liver is an important risk factor for cellular liver injury and biliary tract injury. At a median follow-up of 12 years after cancer diagnosis, 22 out of 123 (17.9%) cases of childhood cancer treated with radiotherapy involving the liver had abnormal ALT and/or γGT levels: 4 received TBI (7.5-12 Gy) and 18 abdominal radiation (9-34 Gy). Tefft 1970 reported a prevalence of abnormal liver enzyme tests of 58% in 88 childhood cancer survivors treated with radiotherapy involving the liver at a mean follow-up of four years after the end of treatment, but it was unclear which liver enzyme tests were performed and how an abnormal test result was defined. The majority of participants were treated with a liver irradiation dose of 25 Gy or more.

Chronic HBV and HCV infection were identified in one multivariable and six univariable analyses as risk factors for hepatic late adverse effects. Acute HBV infection in children has a variable clinical course ranging from asymptomatic state to fulminant hepatitis, with the rate of chronic infection ranging from 90% in neonates to 1% to 5% in adolescents (Kurbegov 2009). Acute infection with HCV tends to cause mild hepatitis, yet chronic infection occurs in approximately 80% of patients (Villano 1999). When chronically infected with HBV or HCV, patients are at risk for liver-related morbidity and mortality from cirrhosis or hepatocellular carcinoma. In a study of Castellino 2004, which investigated the long-term outcomes of chronic HCV infection among survivors of childhood cancer, it was shown that at a median follow-up of 12.4 years, 28.8% of participants had developed mild fibrosis, 35.6% moderate fibrosis, and 13.6% cirrhosis. This study was excluded from this systematic review because the study population consisted solely of hepatitis virus-infected childhood cancer survivors. It should be noted, however, that the importance of chronic HCV infection among childhood cancer survivors is declining as the global prevalence of HCV has dramatically decreased since the introduction of effective screening of blood products in 1992 and 1993 (Hudson 2005).

Higher BMI, metabolic syndrome, alcohol intake, longer follow-up time, and older age at follow-up were also associated with an increased risk of hepatic late adverse effects. Those factors are strongly associated with liver disease in the normal population (Luyckx 2000; Maddrey 2000; Sheen 2002). Although the risk of cellular liver dysfunction in childhood cancer survivors may be a reflection of an aging population prone to developing a higher BMI, and (in a subset) consuming greater units of alcohol, the increased

risk is also attributable to cancer treatment. Previous studies have, for example, shown that survivors of childhood cancer are at increased risk of obesity and metabolic syndrome (Meacham 2005; Meacham 2010).

Other reported risk factors were cranial radiotherapy (in one study significant, in one study not significant), standard-dose asparaginase (compared to low-dose, in one study significant) iron overload (in one study significant, in two studies not significant), fatty liver (steatosis) (in one study significant, in two studies not significant) older age at haematopoietic stem cell transplantation (HSCT) (in one study significant) and the diagnosis of a benign haematological disease (in one study significant); although none of the studies conducted multivariable analyses with adjustment for important prognostic factors and follow-up. Results from univariable analyses that do not take possible confounding factors into account may lead to an overestimation of the prognostic influence of a single variable. Consequently, the results of these studies must be interpreted with caution. No studies exist in which the association between SOS or graft-versus-host disease (GVHD) and hepatic late adverse effects was evaluated. In addition, none of the studies in this systematic review included a control group. A control group would have allowed us to separate out the effects of important risk factors in order to determine the level of causation.

Liver histology is the current gold standard for diagnosing liver damage but is applied conservatively in paediatric patients due to the invasive nature of the test (Saleh 2007). Since only four studies performed liver biopsies, in a selected group of participants with clinical indications, we were not able to analyse histologically-determined hepatic late adverse effects. Consequently, we had to focus on hepatic injury defined by elevated liver enzymes, especially serum ALT level. Although ALT is produced by other organs, it is found mainly in hepatocytes and is considered to be the most reliable and sensitive single marker of acute or subacute liver injury (Kim 2008). Recently, Ruhl 2009 investigated whether elevated ALT levels were associated with an increased risk of all-cause and disease-specific mortality among 14,950 adults from the US population. Although elevated ALT was not associated with all-cause mortality, it did relate to deaths from liver disease. An elevation in ALT was associated with a more than eight-fold increased risk of cause-specific mortality from liver disease. There is, however, still some doubt about the validity of serum ALT as a marker of liver disease. Elevated ALT can be asymptomatic and does not always progress to liver failure or cirrhosis. In addition, liver enzyme levels can be normal while having liver cirrhosis. Especially in the case of chronic HCV infection, normal ALT levels have been found while having liver abnormalities. So normal liver enzyme levels do not exclude the diagnosis of a chronic HCV infection and liver cirrhosis (Field 2008; Kim 2008). Therefore, it is difficult to judge the exact clinical consequence of hepatic late adverse effects as measured in this systematic review. Other parameters which are frequently used for liver function testing are AST, γGT, ALP, bilirubin, and coagulation times (PTT and APTT). Because the studies included in this systematic review mainly reported ALT levels, it was difficult to draw any conclusions on other measures of liver function and their relationship to long-term liver health in childhood cancer survivors.

After assessing the risk of bias of the included studies, which included both internal and external validity, it was obvious that all studies had methodological limitations. However, it should be noted that this assessment focused only on the evaluation of the prevalence of hepatic late adverse effects. Therefore, the quality of the included studies was only judged regarding these items.

Internal validity gives an indication of the bias present in a study and thus how valid the results of a study are. There was an 82% risk of selection bias in studies included in this systematic review. This led to concern that an overestimation of the prevalence of hepatic late adverse effects would exist if patients with a higher risk profile were selected for the study, and an underestimation if patients with a lower risk profile were selected. In addition, the small risk of attrition bias (15%) may lead to an overestimation of the prevalence of hepatic late adverse effects if participants lost to follow-up were in better health than those still under medical surveillance. Conversely, it would lead to an underestimation if participants lost to follow-up were more likely to be suffering from hepatic late adverse effects, for example, because they were more frequently unable to complete the follow-up schedule of the study. Finally, detection bias could lead to an overestimation of the prevalence of hepatic late adverse effects since knowledge of prognostic factors could increase the possibility of classifying participants as having hepatic late adverse effects. All studies in this review reported liver outcomes that were defined by absolute laboratory values. Because this could be interpreted objectively, the blinding of the outcome assessor was not important. In four studies that performed liver biopsies, it was unclear if the outcome assessors were blinded. Another potential bias was the fact that many of the included studies did not mention the actual methods of monitoring. In some studies, all participants had routine surveillance which is much more reliable and less likely to be biased as compared to ad hoc or non-protocolised testing.

The external validity of a study indicates how well the results of the study could be extrapolated to individual participants. There was a moderate risk of reporting bias in studies included in this systematic review. Because the study group was not well-defined in more than half of the included studies, and only a small majority used an objective and precise outcome definition, it is difficult to interpret the results correctly. Although most of the studies reported the length of follow-up, the median duration varied widely from 2.0 years after the end of treatment to 25.1 years since primary cancer diagnosis in studies that reported the median follow-up duration. With short follow-up, it is possible that the injury to the liver may be transient and reversible. With longer follow-up, more participants would be at risk for hepatic late adverse effects. However, it was not clear whether treatment-related increased risks of hepatic late adverse effects would continue to be raised with more prolonged follow-up, or that the risk would level off or even decrease at some point of time. Therefore, cautious interpretation of the results is needed when the study findings are related to individual patients.

Variation in the studies that evaluated the prevalence of hepatic late adverse effects could also be explained by other factors. Differences in the prevalence of hepatic late adverse effects could be a reflection of different risk profiles in the study population. Factors such as chemotherapy type and dose, co-treatment with other hepatotoxic drugs, age at diagnosis, and age at follow-up varied considerably across the studies, which may explain the variation in the prevalence. Moreover, it should be noted that the prevalence of chronic HBV and HCV infection differed between countries and was based on the era of cancer diagnosis (Hudson

2005). In Mediterranean countries, chronic viral hepatitis is more endemic (Baldo 2008) so patients who received blood transfusions in these countries were at higher risk for chronic HBV or HCV infections.

In conclusion, this systematic review showed that the prevalence of hepatic late adverse effects ranged from 5.8% to 52.8% when selecting studies with an adequate outcome definition of ALT above the upper limit of normal, indicating cellular liver injury. One study investigated biliary tract injury defined as γGT above the upper limit of normal and reported a prevalence of 5.3%. In addition, three studies investigated disturbance in biliary function defined as bilirubin above the upper limit of normal and reported prevalences ranging from 0% to 8.7%. Evidence suggests that radiotherapy involving the liver, higher BMI, chronic viral hepatitis, and longer follow-up time or older age at follow-up increase the risk of hepatic late adverse effects. In addition, there may be a suggestion that busulfan, thioguanine, hepatic surgery, higher alcohol intake (> 14 units per week), metabolic syndrome, use of statins, non-Hispanic white ethnicity, and older age at cancer diagnosis increase the risk of hepatic late adverse effects.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review shows that childhood cancer survivors are at risk for hepatic late adverse effects defined as ALT above the upper limit of normal. Evaluation of serum ALT level could be helpful to screen early for hepatic late adverse effects. Abnormalities should initiate additional evaluation and measurement to prevent any further damage. Based on the results of this systematic review, it might be rational to monitor childhood cancer survivors treated with radiotherapy involving the liver, busulfan, thioguanine and/or hepatic surgery. Recommendations about the time interval of evaluation and the importance of other tests cannot be made based on currently available evidence. One should keep in mind: no evidence of effect does not mean evidence of no effect. As more data become available, clinicians will be able to make better-informed decisions regarding the treatment of future childhood cancer patients and to develop targeted follow-up programs for survivors. Since liver disease can be indolent, it might be rational that counselling should be provided regarding preventive behaviours like avoidance of alcohol, immunization against hepatitis A and B, and cautious use of alternative therapies that have a risk of liver injury.

Implications for research

Based on the results of this systematic review, high-quality studies in childhood cancer survivors are needed to: 1) evaluate the exact radiotherapy and chemotherapy threshold doses for developing hepatic late adverse effects; 2) evaluate the possible joint effects of radiation dose and radiation volume on the risk of hepatic late adverse effects; 3) evaluate the impact of aging on the risk of hepatic late adverse effects; 4) evaluate the influence of other determinants on the risk of hepatic late adverse effects, such as haematopoietic stem cell transplant, steatosis, SOS, iron overload, and GVHD; 5) evaluate time trends and associated risk factors for hepatic late adverse effects; 6) evaluate the predictive value of first assessment on hepatic late adverse effects time trends; 7) evaluate the prognostic value of subclinical hepatic late adverse effects for developing clinical disease. In addition, since many of the studies are quite dated and the epidemiology of chronic viral hepatitis has changed, more current data is needed. Ideally, future studies should longitudinally evaluate liver health in all children treated for cancer. Follow-up should be long enough and complete with precise and uniform outcome definitions, including transaminases and synthetic indicators of liver function. The development of imaging modalities which may lead to non-invasive characterisation of the liver also holds promise for this population. While the cancer survivor has many end organ risks after therapy, it remains to be investigated whether the unique regenerative capacity of the liver obviates follow-up for hepatic late adverse effects or whether certain host or therapy exposures lead to threshold effects for late liver injury.

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REFERENCES

References to studies included in this review

Aricò 1994 *{published data only}*

Aricò M, Maggiore G, Silini E, Bono F, Vigano C, Cerino A, et al. Hepatitis C virus infection in children treated for acute lymphoblastic leukemia. *Blood* 1994;**84**:2919-22.

Ballauff 1999 *{published data only}*

Ballauff A, Krahe J, Jansen B, Ross RS, Roggendorf H, Havers W. Chronic liver disease after treatment of malignancies in children [Chronische hepatopathien nach behandlung maligner erkrankungen bei kindern]. *Klinische Pädiatrie* 1999;**211**:49-52.

Bessho 1994 *{published data only}*

Bessho F, Kinumaki H, Yokota S, Hayashi Y, Kobayashi M, Kamoshita S. Liver function studies in children with acute lymphocytic leukemia after cessation of therapy. *Medical and Pediatric Oncology* 1994;**23**:111-5.

Bresters 2008 *{published data only}*

Bresters D, Van Gils IC, Dekker FW, Lankester AC, Bredius RG, Schweizer JJ. Abnormal liver enzymes two years after haematopoietic stem cell transplantation in children: prevalence and risk factors. *Bone Marrow Transplantation* 2008;**41**:27-31.

Chotsampancharoen 2009 *{published data only}*

Chotsampancharoen T, Gan K, Kasow KA, Barfield RC, Hale GA, Leung W. Iron overload in survivors of childhood leukemia after allogeneic hematopoietic stem cell transplantation. *Pediatric Transplantation* 2009;**13**:348-52.

Delvecchio 2017 *{published data only}*

Delvecchio M, Muggeo P, Monteduro M, Lassandro G, Novielli C, Valente F, et al. Non-alcoholic fatty liver disease is associated with early left ventricular dysfunction in childhood acute lymphoblastic leukaemia survivors. *European Journal of Endocrinology* 2017;**176**:111-21.

El-Rashedy 2017 *{published data only}*

El-Rashedy FH, El-Hawy MA, El Hefnawy SM, Mohammed MM. Assessment of obesity and hepatic late adverse effects in the Egyptian survivors of pediatric acute lymphoblastic leukemia: a single center study. *Mediterranean Journal of Hematology and Infectious Diseases* 2017;**9**:e2017026.

French 2012 *{published data only}*

French AE, Irwin MS, Navarro OM, Greenberg M, Nathan PC. Long-term hepatic outcomes in survivors of stage 4S and 4 neuroblastoma in infancy. *Pediatric Blood and Cancer* 2012;**58**:283-8.

Frisk 1998 *{published data only}*

Frisk P, Lonnerholm G, Oberg G. Disease of the liver following bone marrow transplantation in children: incidence, clinical course and outcome in a long-term perspective. *Acta Paediatrica* 1998;**87**:579-83.

Green 2019 *{published data only}*

Green DM, Wang M, Krasin MJ, Srivastava DK, Relling MV, Howell CR, et al. Serum ALT elevations in survivors of childhood cancer. A report from the St. Jude Lifetime Cohort Study. *Hepatology* 2019;**69**:94-106.

Guido 1991 *{published data only}*

Guido M, Rossetti F, Rugge M, Cesaro S, Aneloni V, Ninfo V, et al. Leukemia and liver disease in childhood: clinical and histological evaluation. *Tumori* 1991;**77**:319-22.

Gunn 2016 *{published data only}*

Gunn HM, Emilsson H, Gabriel M, Maguire AM, Steinbeck KS. Metabolic health in childhood cancer survivors: a longitudinal study in a long-term follow-up clinic. *Journal of Adolescent and Young Adult Oncology* 2016;**5**:24-30.

Hudson 2013 *{published data only}*

Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *Journal of the American Medical Association* 2013;**309**:2371-81.

Hyodo 2012 *{published data only}*

Hyodo H, Ishiguro H, Tomita Y, Takakura H, Koike T, Shimizu T, et al. Decreased serum testosterone levels in long-term adult survivors with fatty liver after childhood stem cell transplantation. *Biology of Blood and Marrow Transplantation* 2012;**18**:1119-27.

Jagt 2009 *{published data only}*

Jagt CT, Zuckermann M, Ten Kate F, Taminiau JA, Dijkgraaf MG, Heij H, at al. Veno-occlusive disease as a complication of preoperative chemotherapy for Wilms tumor: a clinico-pathological analysis. *Pediatric Blood and Cancer* 2009;**53**:1211-5.

Landier 2012 *{published data only}*

Landier W, Armenian SH, Lee J, Thomas O, Wong FL, Francisco L, et al. Yield of screening for long-term complications using the children's oncology group long-term follow-up guidelines. *Journal of Clinical Oncology* 2012;**30**:4401-8.

Locasciulli 1983 *{published data only}*

Locasciulli A, Vergani GM, Uderzo C, Jean G, Cattaneo M, Vergani D, et al. Chronic liver disease in children with leukemia in long-term remission. *Cancer* 52;**1983**:1080-7.

Locasciulli 1985 *{published data only}*

Locasciulli A, Alberti A, Rossetti F, Santamaria M, Santoro N, Madon E, et al. Acute and chronic hepatitis in childhood leukemia: a multicentric study from the Italian Pediatric Cooperative Group for Therapy of Acute Leukemia (AIL-AIEOP). *Medical and Pediatric Oncology* 1985;**13**:203-6.

Locasciulli 1991a *{published data only}*

Locasciulli A, Gornati G, Tagger A, Ribero ML, Cavalletto D, Cavalletto L. Hepatitis C virus infection and chronic liver

disease in children with leukemia in long-term remission. *Blood* 1991;**78**:1619-22.

Locasciulli 1997a *{published data only}*

Locasciulli A, Testa M, Pontisso P, Benvegnu L, Fraschini D, Corbetta A, et al. Prevalence and natural history of hepatitis C infection in patients cured of childhood leukemia. *Blood* 1997;**90**:4628-33.

Locasciulli 1997b *{published data only}*

Locasciulli A, Testa M, Valsecchi MG, Vecchi L, Longoni D, Sparano P, et al. Morbidity and mortality due to liver disease in children undergoing allogeneic bone marrow transplantation: a 10-year prospective study. *Blood* 1997;**90**:3799-805.

Matsuzaki 2001 *{published data only}*

Matsuzaki A, Ishii E, Nagatoshi Y, Eguchi H, Koga H, Yanai F, et al. Long-term outcome of treatment with protocols AL841, AL851, and ALHR88 in children with acute lymphoblastic leukemia: results obtained by the Kyushu-Yamaguchi Children's Cancer Study Group. *International Journal of Hematology* 2001;**73**:369-77.

Mulder 2013 *{published data only}*

Mulder RL, Kremer LC, Koot BG, Benninga MA, Knijnenburg SL, Van der Pal HJH, et al. Surveillance of hepatic late adverse effects in a large cohort of long-term survivors of childhood cancer: prevalence and risk factors. *European Journal of Cancer* 2013;**49**:185-93.

Ratner 1986 *{published data only}*

Ratner L, Peylan-Ramu N, Wesley R, Poplack DG. Adverse prognostic influence of hepatitis B virus infection in acute lymphoblastic leukemia. *Cancer* 1986;**58**:1096-100.

Rossetti 1991 *{published data only}*

Rossetti F, Zancan L, Bonato MG, Quaranta E, Rosolen A, Rugge M, et al. Delta virus and childhood leukemia. *Pediatric Hematology and Oncology* 1991;**8**:23-32.

Schempp 2016 *{published data only}*

Schempp A, Lee J, Kearney S, Mulrooney DA, Smith AR. Iron overload in survivors of childhood cancer. *Journal of Pediatric Hematology/Oncology* 2015;**38**:27-31.

Seth 2017 *{published data only}*

Seth R, Singh A, Seth S, Sapra S. Late effects of treatment in survivors of childhood cancers: a single-centre experience. *Indian Journal of Medical Research* 2017;**146**:216-23.

Skou 2014 *{published data only}*

Skou AS, Glosli H, Jahnukainen K, Jarfelt M, Jonmundsson GK, Malmros-Svennilson J, et al. Renal, gastrointestinal, and hepatic late effects in survivors of childhood acute myeloid leukemia treated with chemotherapy only - a NOPHO-AML study. *Pediatric Blood and Cancer* 2014;**61**:1638-43.

Stringer 1995 *{published data only}*

Stringer MD, Hennayake S, Howard ER, Spitz L, Shafford EA, Mieli-Vergani G, et al. Improved outcome for children with hepatoblastoma. *British Journal of Surgery* 1995;**82**:386-91.

Tefft 1970 *{published data only}*

Tefft M, Mitus A, Das L, Vawter GF, Filler RM. Irradiation of the liver in children: review of experience in the acute and chronic phases, and in the intact normal and partially resected. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* 1970;**108**:365-85.

Tomita 2011 *{published data only}*

Tomita Y, Ishiguro H, Yasuda Y, Hyodo H, Koike T, Shimizu T, et al. High incidence of fatty liver and insulin resistance in long-term adult survivors of childhood SCT. *Bone Marrow Transplantation* 2011;**46**:416-25.

Vora 2006 *{published data only}*

Vora A, Mitchell CD, Lennard L, Eden TO, Kinsey SE, Lilleyman J. Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukaemia: a randomised trial. *Lancet* 2006;**368**:1339-48.

Weber 1987 *{published data only}*

Weber BL, Tanyer G, Poplack DG, Reaman GH, Feusner JH, Miser JS, at al. Transient acute hepatotoxicity of high-dose methotrexate therapy during childhood. *NCI Monographs* 1987;**5**:207-12.

References to studies excluded from this review

Adson 1981 *{published data only}*

Adson MA, Weiland LH. Resection of primary solid hepatic tumors. *American Journal of Surgery* 1981;**141**:18-21.

Al-Attar 1986 *{published data only}*

Al-Attar A, Pritchard J, Al-Saleem T. Intensive chemotherapy for non-localised Burkitt's lymphoma. *Archives of Disease in Childhood* 1986;**61**:1013-9.

Amylon 1997 *{published data only}*

Amylon MD, Co JPT, Snyder DS, Donaldson SS, Blume KG, Forman SJ. Allogeneic bone marrow transplant in pediatric patients with high-risk hematopoietic malignancies early in the course of their disease. *Journal of Pediatric Hematology/Oncology* 1997;**19**:54-61.

Asdahl 2016 *{published data only}*

Asdahl PH, Winther JF, Bonnesen TG, De Fine Licht S, Gudmundsdottir T, Holmqvist AS, et al. Gastrointestinal and liver disease in adult life after childhood cancer in Scandinavia: a population-based cohort study. *International Journal of Cancer* 2016;**139**:1501-11.

Atay 2005 *{published data only}*

Atay AA, Kurekci AE, Kesik V, Kilic S, Gulgun M, Ozcan O, et al. Retrospective analysis of children with acute lymphoblastic leukemia [Akut lenfoblastik losemili olgularimizin retrospektif analizi]. *Gulhane Medical Journal* 2005;**47**:183-6.

Avet Loiseau 1991 *{published data only}*

Avet Loiseau H, Hartmann O, Valteau D, McDowell H, Brugieres L, Vassal G, et al. High-dose chemotherapy containing busulfan followed by bone marrow transplantation in 24

children with refractory or relapsed non-Hodgkin's lymphoma. *Bone Marrow Transplantation* 1991;**8**:465-72.

Bacigalupo 1991 *{published data only}*

Bacigalupo A, Van Lint MT, Occhini D, Gualandi F, Lamparelli T, Sogno G, et al. Increased risk of leukemia relapse with high-dose cyclosporine A after allogeneic marrow transplantation for acute leukemia. *Blood* 1991;**77**:1423-8.

Baker 2010 *{published data only}*

Baker KS, Bresters D, Sande JE. The burden of cure: long-term side effects following hematopoietic stem cell transplantation (HSCT) in children. *Pediatric Clinics of North America* 2010;**57**:323-42.

Baker 2010b *{published data only}*

Baker KS, Ness KK, Weisdorf D, Francisco L, Sun CL, Forman S, et al. Late effects in survivors of acute leukemia treated with hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. *Leukemia* 2010;**24**:2039-47.

Balcerska 2000 *{published data only}*

Balcerska A, Aleszewicz-Baranowska J, Adamkiewicz-Drozynska E, Bien E, Sierota D, Kaczorowska B, et al. Cardiotoxic complications in Wilms' tumour survivors after treatment with anthracyclines [Powiklania kardiotoksyczne u pacjentow z guzem wilmsa leczonych antracyklinami]. *Medycyna Wieku Rozwojowego* 2000;**4**:111-9.

Bauditz 2007 *{published data only}*

Bauditz J, Lochs H, Ventz M. Long-term follow-up of patients with suprasellar germinomas [Langzeitverlauf bei Patienten mit suprasellären Germinomen]. *Medizinische Klinik* 2007;**102**:803-8.

Benesch 2001 *{published data only}*

Benesch M, Lackner H, Moser A, Kerbl R, Schwinger W, Oberbauer R, et al. Outcome and long-term side effects after synchronous radiochemotherapy for childhood brain stem gliomas. *Pediatric Neurosurgery* 2001;**35**:173-80.

Benz-Bohm 2010 *{published data only}*

Benz-Bohm G, Hero B, Gossmann A, Simon T, Korber F, Berthold F. Focal nodular hyperplasia of the liver in longterm survivors of neuroblastoma: how much diagnostic imaging is necessary?. *European Journal of Radiology* 2010;**74**:e1-e5.

Berger 2013 *{published data only}*

Berger M, Fernandez-Pineda I, Cabello R, Ramirez-Villar GR, Marquez-Vega C, Nustede R, et al. The relationship between the site of metastases and outcome in children with stage IV Wilms tumor: data from 3 European pediatric cancer institutions. *Journal of Pediatric Hematology and Oncology* 2013;**35**:518-24.

Berjian 1980 *{published data only}*

Berjian RA, Douglass HO Jr, Nava HR, Karakousis C. The role of hepatic artery ligation and dearterialization with infusion chemotherapy in advanced malignancies in the liver. *Journal of Surgical Oncology* 1980;**14**:379-87.

Berman 1980 *{published data only}*

Berman MM, Libbey NP, Foster JH. Hepatocellular carcinoma. Polygonal cell type with fibrous stroma - an atypical variant with a favorable prognosis. *Cancer* 1980;**46**:1448-55.

Bernard 2014 *{published data only}*

Bernard F, Auquier P, Herrmann I, Contet A, Poiree M, Demeocq F, et al. Health status of childhood leukemia survivors who received hematopoietic cell transplantation after BU or TBI: an LEA study. *Bone Marrow Transplantation* 2014;**49**:709-16.

Bernstein 1993 *{published data only}*

Bernstein D, Baum D, Berry G, Dahl G, Weiss L, Starnes VA, et al. Neoplastic disorders after pediatric heart transplantation. *Circulation* 1993;**88**:230-7.

Bhatia 2009 *{published data only}*

Bhatia S, Constine LS. Late morbidity after successful treatment of children with cancer. *Cancer Journal* 2009;**15**:174-80.

Bhatia 2012 *{published data only}*

Bhatia S. Long-term complications of therapeutic exposures in childhood: lessons learned from childhood cancer survivors. *Pediatrics* 2012;**130**:1141-3.

Blum 2002 *{published data only}*

Blum W, Brown R, Lin HS, Zehnbauer B, Khoury H, Goodnough LT, et al. Low-dose (550 cGy), single-exposure total body irradiation and cyclophosphamide: consistent, durable engraftment of related-donor peripheral blood stem cells with low treatment-related mortality and fatal organ toxicity. *Biology of Blood and Marrow Transplantation* 2002;**8**:608-18.

Bonnesen 2018 *{published data only}*

Bonnesen TG, Winther JF, Andersen KK, Asdahl PH, De Fine Licht S, Gudmundsdottir T, et al. Liver diseases in adult life after childhood cancer in Scandinavia (ALiCCS): a population-based cohort study of 32,839 one-year survivors. *International Journal of Cancer* 2018;**142**:702-8.

Broxson 2005 *{published data only}*

Broxson EH, Dole M, Wong R, Laya BF, Stork L. Portal hypertension develops in a subset of children with standard risk acute lymphoblastic leukemia treated with oral 6-thioguanine during maintenance therapy. *Pediatric Blood and Cancer* 2005;**44**:226-31.

Brunet 2001 *{published data only}*

Brunet S, Urbano-Ispizua A, Ojeda E, Ruiz D, Moraleda JM, Diaz MA, et al. Favourable effect of the combination of acute and chronic graft-versus-host disease on the outcome of allogeneic peripheral blood stem cell transplantation for advanced haematological malignancies. *British Journal of Haematology* 2001;**114**:544-50.

Carter 1997 *{published data only}*

Carter TL, Cole CH, Mews CF, Price PJ, Baker DL. The prevalence of hepatitis C in survivors of paediatric malignancy. *Journal of Paediatrics and Child Health* 1997;**33**:238-41.

Cassady 1979 *{published data only}*

Cassady JR, Carabell SC, Jaffe N. Chemotherapy-irradiation related hepatic dysfunction in patients with Wilms' tumor. *Frontiers of Radiation Therapy and Oncology* 1979;**13**:147-60.

Castellino 2010 *{published data only}*

Castellino S, Muir A, Shah A, Shope S, McMullen K, Ruble K, et al. Hepato-biliary late effects in survivors of childhood and adolescent cancer: a report from the Children's Oncology Group. *Pediatric Blood and Cancer* 2010;**54**:663-9.

Cavo 1998 *{published data only}*

Cavo M, Bandini G, Benni M, Gozzetti A, Ronconi S, Rosti G, et al. High-dose busulfan and cyclophosphamide are an effective conditioning regimen for allogeneic bone marrow transplantation in chemosensitive multiple myeloma. *Bone Marrow Transplantation* 1998;**22**:27-32.

Cesaro 1997 *{published data only}*

Cesaro S, Petris MG, Rossetti F, Cusinato R, Pipan C, Guido M, et al. Chronic hepatitis C virus infection after treatment for pediatric malignancy. *Blood* 1997;**90**:1315-20.

Chao 1993 *{published data only}*

Chao NJ, Stein AS, Long GD, Negrin RS, Amylon MD, Wong RM, et al. Busulfan/etoposide - Initial experience with a new preparatory regimen for autologous bone marrow transplantation in patients with acute nonlymphoblastic leukemia. *Blood* 1993;**81**:319-23.

Cheng 2005 *{published data only}*

Cheng HY, Chu CH, Chang WH, Hsu TC, Lin SC, Liu CC, et al. Clinical analysis of multiple primary malignancies in the digestive system: a hospital-based study. *World Journal of Gastroenterology* 2005;**11**:4215-9.

Cheuk 2008 *{published data only}*

Cheuk DK, Lee TL, Chiang AK, Ha SY, Chan GC. Autologous hematopoietic stem cell transplantation for high-risk brain tumors in children. *Journal of Neuro-Oncology* 2008;**86**:337-47.

Chou 1996 *{published data only}*

Chou RH, Wong GB, Kramer JH, Wara DW, Matthay KK, Crittenden MR, et al. Toxicities of total-body irradiation for pediatric bone marrow transplantation. *International Journal of Radiation Oncology, Biology, Physics* 1996;**34**:843-51.

Christopherson 2014 *{published data only}*

Christopherson KM, Rotondo RL, Bradley JA, Pincus DW, Wynn TT, Fort JA, et al. Late toxicity following craniospinal radiation for early-stage medulloblastoma. *Acta Oncologica* 2014;**53**:471-80.

Christosova 2005 *{published data only}*

Christosova I, Velev M, Starbanov I, Bobev D, Konstantinov D, Brancov O. Hepatoblastoma - treatment results. *Pediatriya* 2005;**45**:62-3.

Claviez 1996 *{published data only}*

Claviez A, Hero B, Schneppenheim R, Berthold F. Hepatopathy in patients with stage 4S neuroblastoma [Hepatopathie bei patienten mit neuroblastom stadium 4S]. *Klinische Pädiatrie* 1996;**208**:221-8.

Colsky 1955 *{published data only}*

Colsky J, Greenspan EM, Warren TN. Hepatic fibrosis in children with acute leukemia after therapy with folic acid antagonists. *A.M.A. Archives of Pathology* 1955;**59**:198-206.

Condren 2005 *{published data only}*

Condren M, Lubsch L, Vats TS. Long-term follow-up of survivors of childhood cancer. *Indian Journal of Pediatrics* 2005;**72**:39-43.

Coura 2016 *{published data only}*

Coura CF, Modesto PC. Impact of late radiation effects on cancer survivor children: an integrative review. *Einstein (Sao Paulo, Brazil)* 2016;**14**:71-6.

Damon 2006 *{published data only}*

Damon L, Rugo H, Tolaney S, Navarro W, Martin IT, Ries C, et al. Cytoreduction of lymphoid malignancies and mobilization of blood hematopoietic progenitor cells with high doses of cyclophosphamide and etoposide plus filgrastim. *Biology of Blood and Marrow Transplantation* 2006;**12**:316-24.

Deeg 1986 *{published data only}*

Deeg HJ, Sullivan KM, Buckner CD, Storb R, Appelbaum FR, Clift RA, et al. Marrow transplantation for acute nonlymphoblastic leukemia in first remission: toxicity and long-term follow-up of patients conditioned with single dose or fractionated total body irradiation. *Bone Marrow Transplantation* 1986;**1**:151-7.

De Fine Licht 2017 *{published data only}*

De Fine Licht S, Rugbjerg K, Gudmundsdottir T, Bonnesen TG, Asdahl PH, Holmqvist AS, et al. Long-term inpatient disease burden in the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study: a cohort study of 21,297 childhood cancer survivors. *PLOS Medicine* 2017;**14**:e1002296.

Delvecchio 2015 *{published data only}*

Delvecchio M, Luce V, Monteduro M, Giordano P, Muggeo P, Santoro N, et al. Metabolic syndrome in childhood acute lymphoblastic leukaemia survivors. *Hormone Research in Paediatrics* 2015;**1**:405.

Dibenedetto 1994 *{published data only}*

Dibenedetto SP, Ragusa R, Sciacca A, Di Cataldo A, Miraglia V, D'Amico S, et al. Incidence and morbidity of infection by hepatitis C virus in children with acute lymphoblastic leukaemia. *European Journal of Pediatrics* 1994;**153**:271-5.

Dunkel 1998 *{published data only}*

Dunkel IJ, Boyett JM, Yates A, Rosenblum M, Garvin JH Jr, Bostrom BC, et al. High-dose carboplatin, thiotepa, and etoposide with autologous stem-cell rescue for patients with recurrent medulloblastoma. *Journal of Clinical Oncology* 1998;**16**:222-8.

Dupuis-Girod 1996 *{published data only}*

Dupuis-Girod S, Hartmann O, Benhamou E, Doz F, Mechinaud F, Bouffet E, et al. Will high dose chemotherapy followed

by autologous bone marrow transplantation supplant cranio-spinal irradiation in young children treated for medulloblastoma?. *Journal of Neuro-Oncology* 1996;**27**:87-98.

El-Raziky 2015 *{published data only}*

El-Raziky MS, Halawa EF, Draz IH, Ali MS. Natural history and response to treatment of HCV infection among Egyptian survivors of childhood malignancy. *Pediatric Hematology and Oncology* 2015;**32**:138-45.

Evans 1980 *{published data only}*

Evans AE, Chatten J, D'Angio GJ, Gerson JM, Robinson J, Schnaufer L. A review of 17 IV-S neuroblastoma patients at the children's hospital of Philadelphia. *Cancer* 1980;**45**:833-9.

Evans 1982 *{published data only}*

Evans AE, Land VJ, Newton WA, Randolph JG, Sather HN, Tefft M. Combination chemotherapy (vincristine, adriamycin, cyclophosphamide, and 5-fluorouracil) in the treatment of children with malignant hepatoma. *Cancer* 1982;**50**:821-6.

Evans 1990 *{published data only}*

Evans RG, Kimler BF, Morantz RA, Vats TS, Gemer LS, Liston V, et al. A phase I/II study of the use of fluosol as an adjuvant to radiation therapy in the treatment of primary high-grade brain tumors. *International Journal of Radiation Oncology, Biology, Physics* 1990;**19**:415-20.

Evans 1993 *{published data only}*

Evans RG, Kimler BF, Morantz RA, Batnitzky S. Lack of complications in long-term survivors after treatment with fluosol(R) and oxygen as an adjuvant to radiation therapy for high-grade brain tumors. *International Journal of Radiation Oncology, Biology, Physics* 1993;**26**:649-52.

Exelby 1975 *{published data only}*

Exelby PR, Filler RM, Grosfeld JL. Liver tumors in children in the particular reference to hepatoblastoma and hepatocellular carcinoma: American Academy of Pediatrics Surgical Section Survey - 1974. *Journal of Pediatric Surgery* 1975;**10**:329-37.

Fabbri 1994 *{published data only}*

Fabbri A, Motta E, Ferrari S, Longhi C, Marchi E, Bacci G, et al. High-dose methotrexate treatment and liver function in patients with osteosarcoma. *Journal of Internal Medicine* 1994;**236**:209-14.

Farthing 1982 *{published data only}*

Farthing MJ, Clark ML, Sloane JP, Powles RL, McElwain TJ. Liver disease after bone marrow transplantation. *Gut* 1982;**23**:465-74.

Fink 1993 *{published data only}*

Fink FM, Hocker-Schulz S, Mor W, Puchhammer-Stockl E, Hofmann H, Zoubek A, et al. Association of hepatitis C virus infection with chronic liver disease in paediatric cancer patients. *European Journal of Pediatrics* 1993;**152**:490-2.

Fiorreda 2010 *{published data only}*

Fioredda F, Moser A, Bertoluzzo L, Lackner H, Giacchino R, LaSpina M, et al. Natural course of HCV infection in childhood cancer survivors. *Supportive Care in Cancer* 2010;**18**:1413-20.

Forbes 1995 *{published data only}*

Forbes GM, Davies JM, Herrmann RP, Collins BJ. Liver disease complication bone marrow transplantation: a clinical audit. *Journal of Gastroenterology and Hepatology* 1995;**10**:1-7.

Frickhofen 1994 *{published data only}*

Frickhofen N, Wiesneth M, Jainta C, Hertenstein B, Heymer B, Bianchi L, et al. Hepatitis C virus infection is a risk factor for liver failure from veno-occlusive disease after bone marrow transplantation. *Blood* 1994;**83**:1998-2004.

Friedrichs 2010 *{published data only}*

Friedrichs B, Tichelli A, Bacigalupo A, Russel NH, Ruutu T, Shapira MY, et al. Long-term outcome and late effects in patients transplanted with mobilised blood or bone marrow: a randomised trial. *Lancet Oncology* 2010;**11**:331-8.

Gandola 2009 *{published data only}*

Gandola L, Massimino M, Cefalo G, Solero C, Spreafico F, Pecori E, et al. Hyperfractionated accelerated radiotherapy in the Milan strategy for metastatic medulloblastoma. *Journal of Clinical Oncology* 2009;**27**:566-71.

Ganjoo 2006 *{published data only}*

Ganjoo K, An C, Robertson M, Gordon L, Sen J, Weisenbach J, et al. Rituximab, bevacizumab and CHOP (RA-CHOP) in untreated diffuse large B-cell lymphoma: safety, biomarker and pharmacokinetic analysis. *Leukemia and Lymphoma* 2006;**47**:998-1005.

Ghosh 2017 *{published data only}*

Ghosh J, Bajpai J. Chemotherapy for osteosarcoma: adverse effects and remedial measures. *Pediatric Hematology Oncology Journal* 2017;**2**:41-7.

Glick 2000 *{published data only}*

Glick RD, Nadler EP, Blumgart LH, La Quaglia MP. Extended left hepatectomy (left hepatic trisegmentectomy) in childhood. *Journal of Pediatric Surgery* 2000;**35**:303-7.

Gluckman 1979 *{published data only}*

Gluckman E, Devergie A, Dutreix A, Dutreix J, Boiron M, Bernard J. Total body irradiation in bone marrow transplantation. Hopital Saint-Louis results. *Pathologie et Biologie* 1979;**27**:349-52.

Goldsby 2011 *{published data only}*

Goldsby R, Chen Y, Raber S. Survivors of childhood cancer have increased risk of gastrointestinal complications later in life. *Gastroenterology* 2011;**140**:1464-71.

Gonzalez-Crussi 1982 *{published data only}*

Gonzalez-Crussi F, Upton MP, Maurer HS. Hepatoblastoma. Attempt at characterization of histologic subtypes. *American Journal of Surgical Pathology* 1982;**6**:599-612.

Greenfield 2006 *{published data only}*

Greenfield DM, Wright J, Brown JE, Hancock BW, Davies HA, O'Toole L, et al. High incidence of late effects found in Hodgkin's lymphoma survivors, following recall for breast cancer screening. *British Journal of Cancer* 2006;**94**:469-72.

Grill 1996 *{published data only}*

Grill J, Kalifa C, Doz F, Schoepfer C, Sainte-Rose C, Couanet D, et al. A high-dose busulfan-thiotepa combination followed by autologous bone marrow transplantation in childhood recurrent ependymoma. A phase-II study. *Pediatric Neurosurgery* 1996;**25**:7-12.

Grosfeld 1976 *{published data only}*

Grosfeld JL, Fitzgerald JF, Wagner VM, Newton WA, Baehner RL. Portal hypertension in infants and children with histiocytosis X. *American Journal of Surgery* 1976;**131**:108-13.

Gutjahr 1980 *{published data only}*

Gutjahr P. The condition of long-term survivors and patients cured of childhood neoplasms [Langzeit-Uberlebenden und Geheilter nach bosartigen Neubildungen im Kindesalter]. *Fortschritte der Medizin* 1980;**98**:289-92.

Haddy 1998 *{published data only}*

Haddy TB, Adde MA, McCalla J, Domanski MJ, Datiles M, Meehan SC, et al. Late effects in long-term survivors of high-grade non-Hodgkin's lymphomas. *Journal of Clinical Oncology* 1998;**16**:2070-9.

Haddy 2009 *{published data only}*

Haddy TB, Mosher RB, Reaman GH. Late effects in long-term survivors after treatment for childhood acute leukemia. *Clinical Pediatrics* 2009;**48**:601-8.

Hadley 2002 *{published data only}*

Hadley GP, Govender D, Landers G. Malignant solid tumours in neonates: an African perspective. *Pediatric Surgery International* 2002;**18**:653-7.

Halonen 2003 *{published data only}*

Halonen P, Mattila J, Ruuska T, Salo MK, Mäkipernaa A. Liver histology after current intensified therapy for childhood acute lymphoblastic leukemia: microvesicular fatty change and siderosis are the main findings. *Medical and Pediatric Oncology* 2003;**40**:148-54.

Hanks 1980 *{published data only}*

Hanks JB, Meyers WC, Filston HC, Killenberg PG, Jones RS. Surgical resection for benign and malignant liver disease. *Annals of Surgery* 1980;**191**:584-92.

Harrison 1996 *{published data only}*

Harrison P, Neilson JR, Marwah SS, Madden L, Bareford D, Milligan DW. Role of non-transferrin bound iron in iron overload and liver dysfunction in long term survivors of acute leukaemia and bone marrow transplantation. *Journal of Clinical Pathology* 1996;**49**:853-6.

Hatanaka 1994 *{published data only}*

Hatanaka H, Nakagawa Y. Clinical results of long-surviving brain tumor patients who underwent boron neutron capture therapy. *International Journal of Radiation Oncology, Biology, Physics* 1994;**28**:1061-6.

Haupt 2004 *{published data only}*

Haupt R, Nanduri V, Calevo MG, Bernstrand C, Braier JL, Broadbent V, et al. Permanent consequences in Langerhans cell histiocytosis patients: a pilot study from the Histiocyte Society - Late Effects Study Group. *Pediatric Blood and Cancer* 2004;**42**:438-44.

Hedrick 2004 *{published data only}*

Hedrick HL, Flake AW, Crombleholme TM, Howell LJ, Johnson MP, Wilson RD, et al. Sacrococcygeal teratoma: prenatal assessment, fetal intervention, and outcome. *Journal of Pediatric Surgery* 2004;**39**:430-8.

Hegewald 1982 *{published data only}*

Hegewald G, Reddemann H, Barenwald G, Schwanengel H. Electron microscopic findings in the livers of long-term survivors among child tumor patients after polychemotherapy [Elektronenmikroskopische leberfunde bei langzeitüberlebenden tumorpatienten im kindesalter nach polychemotherapie]. *Archiv für Geschwulstforschung* 1982;**52**:397-405.

Henderson 2008 *{published data only}*

Henderson T, Levine J, Patel S, Oeffinger KC. A risk-based approach to the care of survivors of childhood cancer: 3 case studies. *Consultant* 2008;**48**:443-5.

Hjern 2007 *{published data only}*

Hjern A, Lindblad F, Boman KK. Disability in adult survivors of childhood cancer: a Swedish national cohort study. *Journal of Clinical Oncology* 2007;**25**:5262-6.

Ho 2004 *{published data only}*

Ho GT, Parker A, MacKenzie JF, Morris AJ, Stanley AJ. Abnormal liver function tests following bone marrow transplantation: aetiology and role of liver biopsy. *European Journal of Gastroenterology and Hepatology* 2004;**16**:157-62.

Hoffmann 2015 *{published data only}*

Hoffmann A, Bootsveld K, Gebhardt U, Daubenbuchel AM, Sterkenburg AS, Muller HL. Nonalcoholic fatty liver disease and fatigue in long-term survivors of childhood-onset craniopharyngioma. *European Journal of Endocrinology* 2015;**173**:389-97.

Hollard 1980 *{published data only}*

Hollard D, Sotto JJ, Berthier R, Leger J, Michallet M. High rate of long-term survivals in AML treated by chemotherapy and androgenotherapy: a pilot study. *Cancer* 1980;**45**:1540-8.

Holschneider 1977 *{published data only}*

Holschneider AM, Geiger H, Bolkenius N, Janka G, Lampert F. Neuroblastoma: paraneoplastic diseases and late complications. *Monatsschrift fur Kinderheilkunde* 1977;**125**:69-73.

Horowitz 1993 *{published data only}*

Horowitz ME, Kinsella TJ, Wexler LH, Belasco J, Triche T, Tsokos M, et al. Total-body irradiation and autologous bone marrow transplant in the treatment of high-risk Ewing's

sarcoma and rhabdomyosarcoma. *Journal of Clinical Oncology* 1993;**11**:1911-8.

Hutter 1960 *{published data only}*

Hutter RVP, Shipkey FH, Tan CTC, Murphy ML, Chowdhury M. Hepatic fibrosis in children with acute leukemia: a complication of therapy. *Cancer* 1960;**13**:288-307.

Ingold 1965 *{published data only}*

Ingold JA, Reed GB, Kaplan HS, Bagshaw MA. Radiation hepatitis. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* 1965;**93**:200-8.

Isaacs 2008 *{published data only}*

Isaacs H Jr. Fetal hydrops associated with tumors. *American Journal of Perinatology* 2008;**25**:43-68.

Ivantes 2004 *{published data only}*

Ivantes CAP, Amarante H, Ioshii SO, Pasquini R. Hepatitis C virus in long-term bone marrow transplant survivors. *Bone Marrow Transplantation* 2004;**33**:1181-5.

Jaffe 1975 *{published data only}*

Jaffe N. Non-oncogenic sequelae of cancer chemotherapy. *Radiology* 1975;**114**:167-73.

Jagannathan 2004 *{published data only}*

Jagannathan J, Petit JH, Balsara K, Hudes R, Chin LS. Long-term survival after gamma knife radiosurgery for primary and metastatic brain tumors. *American Journal of Clinical Oncology: Cancer Clinical Trials* 2004;**27**:441-4.

Jenkins 2013 *{published data only}*

Jenkins A. Late effects of chemotherapy for childhood cancer. *2013* Paediatrics and Child Health (United Kingdom);**23**:545-9.

Jirtle 1990 *{published data only}*

Jirtle RL, Anscher MS, Alati T. Radiation sensitivity of the liver. *Advances in Radiation Biology* 1990;**14**:269-311.

Jung 2017 *{published data only}*

Jung SY, Lee YJ, Lee HJ, Lee YA, Moon JS, Ko JS, et al. Nonalcoholic fatty liver disease in long-term survivors of childhood-onset craniopharyngioma. *Annals of Pediatric Endocrinology and Metabolism* 2017;**22**:189-96.

Kamani 1996 *{published data only}*

Kamani N, August CS, Bunin N, Leahey A, Bayever E, Goldwein J, et al. A study of thiotepa, etoposide and fractionated total body irradiation as a preparative regimen prior to bone marrow transplantation for poor prognosis patients with neuroblastoma. *Bone Marrow Transplantation* 1996;**17**:911-6.

Kamble 2006 *{published data only}*

Kamble R, Mims M. Iron-overload in long-term survivors of hematopoietic transplantation. *Bone Marrow Transplantation* 2006;**37**:805-6.

Kaste 1999 *{published data only}*

Kaste SC, Gronemeyer SA, Hoffer FA, Mandrell BN, Wilimas JA. Pilot study of noninvasive detection of venous occlusions from central venous access devices in children treated for acute lymphoblastic leukemia. *Pediatric Radiology* 1999;**29**:570-4.

Kazanowska 2004 *{published data only}*

Kazanowska B, Reich A, Reich M, Balcerska A, Balwierz W, Bodalski J, et al. Remaining problems and controversies in the management of childhood head and neck soft tissue sarcomas: retrospective (national) multicenter study of the Polish Pediatric Solid Tumors Group. *Pediatric Hematology and Oncology* 2004;**21**:349-62.

Khouri 2002 *{published data only}*

Khouri IF, Keating MJ, Saliba RM, Champlin RE. Long-term follow-up of patients with CLL treated with allogeneic hematopoietic transplantation. *Cytotherapy* 2002;**4**:217-21.

Kim 2000 *{published data only}*

Kim BK, Chung KW, Sun HS, Min WS, Kang CS, Sim SI, et al. Liver disease during the first post-transplant year in bone marrow transplantation recipients: retrospective study. *Bone Marrow Transplantation* 2000;**26**:193-7.

Kopp 2012 *{published data only}*

Kopp LM, Gupta P, Pelayo-Katsanis L, Wittman B, Katsanis E. Late effects in adult survivors of pediatric cancer: a guide for the primary care physician. *American Journal of Medicine* 2012;**125**:636-41.

Kotz 1982 *{published data only}*

Kotz R, Plattner E, Ramach W, Flener R, Bodo G. Interferon/ controlled study in 3-year survival of patients with osteosarcoma [Verträglichkeitsprüfung von humanem Lymphoblasten-Interferon. Kontrollierte Studie bei 8 Osteosarkom-Patienten mit 3-Jahres-Überleben]. *Arzneimittel-Forschung* 1982;**32**:446-8.

Kremens 2002 *{published data only}*

Kremens B, Gruhn B, Klingebiel T, Hasan C, Laws HJ, Koscielniak E, et al. High-dose chemotherapy with autologous stem cell rescue in children with nephroblastoma. *Bone Marrow Transplantation* 2002;**30**:893-8.

Kudo 1996 *{published data only}*

Kudo T, Morishima T, Tsuzuki K, Orito E, Mizokami M. Hepitits G virus in immunosuppressed paediatric allograft recipients. *Lancet* 1996;**348**:751.

Lackner 2000 *{published data only}*

Lackner H, Benesch M, Schagerl S, Kerbl R, Schwinger W, Urban C. Prospective evaluation of late effects after childhood cancer therapy with a follow-up over 9 years. *European Journal of Pediatrics* 2000;**159**:750-8.

Lackner 2007 *{published data only}*

Lackner H, Moser A, Sovinz P, Benesch M, Schwinger W, Urban C. Long-term care of young adults surviving childhood cancer - where do we go? [Langzeitbetreuung junger Erwachsener nach Krebserkrankung imKindesalter – Wohin führt der Weg?]. *Wiener Klinische Wochenschrift* 2007;**119**:361-4.

Ladenstein 1997 *{published data only}*

Ladenstein R, Pearce R, Hartmann O, Patte C, Goldstone T, Philip T. High-dose chemotherapy with autologous bone marrow rescue in children with poor-risk Burkitt's lymphoma: a report from the European lymphoma bone marrow transplantation registry. *Blood* 1997;**90**:2921-30.

Lee 2016 *{published data only}*

Lee YY, Liang ML, Chen HH, Chang FC, Chen YW, Wong TT. Multidisciplinary treatment preserved hypothalamic-pituitary axis function of craniopharyngiomas in children. *Neuro-Oncology* 2016;**18 (Supplement 3)**:III18.

Leonardi 2003 *{published data only}*

Leonardi S, La Spina M, La Rosa M, Schiliro G. Prolylhydroxylase and procollagen type III in long-term survivors of acute lymphoblastic leukemia (ALL): a biochemical approach to HCV-related liver disease. *Medical and Pediatric Oncology* 2003;**41**:17-20.

Leung 2000 *{published data only}*

Leung W, Hudson MM, Strickland DK, Phipps S, Srivastava DK, Ribeiro RC, et al. Late effects of treatment in survivors of childhood acute myeloid leukemia. *Journal of Clinical Oncology* 2000;**18**:3273-9.

Levitt 2004 *{published data only}*

Levitt GA, Platt KA, De Byrne R, Sebire N, Owens CM. 4S neuroblastoma: the long-term outcome. *Pediatric Blood and Cancer* 2004;**43**:120-5.

Levy 2015 *{published data only}*

Levy A, Martelli H, Fayech C, Minard-Colin V, Dumas I, Gensse MC, et al. Late toxicity of brachytherapy after female genital tract tumors treated during childhood: prospective evaluation with a long-term follow-up. *Radiotherapy and Oncology* 2015;**117**:206-12.

Lindsay 2016 *{published data only}*

Lindsay R, Saliba R, Choi H, Ping Z, Ramlal R, Alousi AM, et al. Transfusion history is the most significant predictor of iron overload after allogeneic stem cell transplantation. *Biology of Blood and Marrow Transplantation* 2016;**1**:S336-7.

Ljungman 1995 *{published data only}*

Ljungman P, Johansson N, Aschan J, Glaumann H, Lonnqvist B, Ringden O, et al. Long-term effects of hepatitis C virus infection in allogeneic bone marrow transplant recipients. *Blood* 1995;**86**:1614-8.

Locasciulli 1989 *{published data only}*

Locasciulli A, Bacigalupo A, Alberti A, Van Lint MT, Uderzo C, Marmont AM, et al. Predictability before transplant of hepatic complications following allogeneic bone marrow transplantation. *Transplantation* 1989;**48**:68-72.

Locasciulli 1990a *{published data only}*

Locasciulli A, Bacigalupo A, Van Lint MT, Mura R, Masera G, Tagger G, et al. Hepatitis C virus (HCV) infection in patients with haematological malignancies treated with chemotherapy or bone marrow transplantation (BMT). *Experimental Hematology* 1990;**18**:696.

Locasciulli 1990b *{published data only}*

Locasciulli A, Uderzo C, Pirola A, Masera G, Portmann B, Alberti A. Pattern of liver disease following high-dose cytosine arabinoside (HDARAC) therapy in children with acute myeloid leukemia. *Leukemia and Lymphoma* 1990;**2**:229-33.

Locasciulli 1991b *{published data only}*

Locasciulli A, Bacigalupo A, Van Lint MT, Tagger A, Uderzo C, Portmann B, et al. Hepatitis C virus infection in patients undergoing allogeneic bone marrow transplantation. *Transplantation* 1991;**52**:315-8.

Locasciulli 1993 *{published data only}*

Locasciulli A, Cavalletto D, Pontisso P, Cavalletto L, Scovena E, Uderzo C, et al. Hepatitis C virus serum markers and liver disease in children with leukemia during and after chemotherapy. *Blood* 1993;**82**:2564-7.

Locasciulli 1995 *{published data only}*

Locasciulli A, Alberti A. Hepatitis C virus serum markers and liver disease in children with leukemia. *Leukemia and Lymphoma* 1995;**17**:245-9.

Lockney 2016 *{published data only}*

Lockney NA, Friedman DN, Wexler LH, Sklar CA, Casey DL, Wolden SL. Late toxicities of intensity-modulated radiation therapy for head and neck rhabdomyosarcoma. *Pediatric Blood and Cancer* 2016;**63**:1608-14.

Lucas 2017 *{published data only}*

Lucas JT, Fernandez-Pineda I, Tinkle CL, Bishop MW, Kaste SC, Heda R, et al. Late toxicity and outcomes following radiation therapy for chest wall sarcomas in pediatric patients. *Practical Radiation Oncology* 2017;**7**:411-17.

MacDonald 2010 *{published data only}*

MacDonald T. Pediatric cancer: a comprehensive review. Part I: Biology, epidemiology, common tumours, principles of treatment and late effects. *Canadian Pharmacists Journal* 2010;**143**:176-83.

Maggiore 1982 *{published data only}*

Maggiore G, Siena S, Prandi M. Hepatitis B and acute lymphoblastic leukemia. *Journal of Pediatrics* 1982;**101**:156.

Maguire 2002 *{published data only}*

Maguire AM, Vowels MR, Russell S, Cohn RJ, Cole C, Saxon B, et al. Allogeneic bone marrow transplant improves outcome for juvenile myelomonocytic leukaemia. *Journal of Paediatrics and Child Health* 2002;**38**:166-9.

Martinez 1997 *{published data only}*

Martinez C, Carreras E, Sierra J, Rovira M, Urbano-Ispizua A, Viguria MC, et al. Second allogeneic progenitor cell transplantation for leukemia relapse: results in 10 patients [Segundo trasplante alogénico de progenitores hematopoyéticos como tratamiento de la recaída leucémica: resultados en 10 pacientes]. *Medicina Clinica* 1997;**109**:401-5.

Masera 1981 *{published data only}*

Masera G, Locasciulli A, Jean G, Jankovic M, Rossi MR, Recchia M, et al. Hepatitis B and childhood acute lymphoblastic leukemia. *Journal of Pediatrics* 1981;**99**:98-100.

McBride 1976 *{published data only}*

McBride CM. Primary carcinoma of the liver. *Surgery* 1976;**80**:322-7.

McDonald 2010 *{published data only}*

McDonald GB. Hepatobiliary complications of hematopoietic cell transplantation, 40 years on. *Hepatology* 2010;**51**:1450-60.

McIntosh 1977 *{published data only}*

McIntosh S, Davidson DL, O'Brien RT, Pearson HA. Methotrexate hepatotoxicity in children with leukemia. *Journal of Pediatrics* 1977;**90**:1019-21.

McKay 1996 *{published data only}*

McKay PJ, Murphy JA, Cameron S, Burnett AK, Campbell M, Tanse P, et al. Iron overload and liver dysfunction after allogeneic or autologous bone marrow transplantation. *Bone Marrow Transplantation* 1996;**17**:63-6.

Meadows 1992 *{published data only}*

Meadows AT, Gallagher JA, Bunin GR. Late effects of early childhood cancer therapy. *British Journal of Cancer* 1992;**66 Suppl**:92-5.

Meeske 2015 *{published data only}*

Meeske KA, Ji L, Freyer DR, Gaynon P, Ruccione K, Butturini A, et al. Comparative toxicity by sex among children treated for acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Pediatric Blood and Cancer* 2015;**62**:2140-9.

Mitrou 1990 *{published data only}*

Mitrou PS, Fischer C, Szepesi S, Heimer K. Results of therapy in Hodgkin's disease [Therapieergebnisse beim Morbus Hodgkin]. *Deutsche Medizinische Wochenschrift* 1990;**115**:1783-9.

Mizumoto 2017 *{published data only}*

Mizumoto M, Murayama S, Akimoto T, Demizu Y, Fukushima T, Ishida Y, et al. Long-term follow-up after proton beam therapy for pediatric tumors: a Japanese national survey. *Cancer Science* 2017;**108**:444-7.

Mohammed 2017 *{published data only}*

Mohammed M, Carpenter P, Park, J, Baker K. Late effects in high risk neuroblastoma survivors treated with high dose chemotherapy and stem cell rescue. *Pediatric Blood and Cancer* 2017;**64 (Supplement 1)**:S73.

Mohapatra 2016 *{published data only}*

Mohapatra S, Bansal D, Bhalla AK, Verma Attri S, Sachdeva N, Trehan A, et al. Is there an increased risk of metabolic syndrome among childhood acute lymphoblastic leukemia survivors? A developing country experience. *Pediatric Hematology and Oncology* 2016;**33**:136-49.

Moore 1995 *{published data only}*

Moore SW, Kaschula ROC, Albertyn R, Rode H, Millar AJW, Karabus C. The outcome of solid tumors occuring in the neonatal period. *Pediatric Surgery International* 1995;**10**:366-70.

Morrow 1982 *{published data only}*

Morrow CE, Grage TB, Sutherland DE, Najarian JS. Hepatic resection for secondary neoplasms. *Surgery* 1982;**92**:610-4.

Murthy 1978 *{published data only}*

Murthy TV, Irving IM, Lister J. Massive adrenal hemorrhage in neonatal neuroblastoma. *Journal of Pediatric Surgery* 1978;**13**:31-4.

Myers 1995 *{published data only}*

Myers B, Irving W, Hollingsworth R, Readett D, Lilleyman JS, Dolan G. Hepatitis C virus infection in multi-transfused children with haematological malignancy. *British Journal of Haematology* 1995;**91**:480-2.

Myers 2013 *{published data only}*

Myers KC, Lawrence J, Marsh RA, Davies SM, Jodele S. High-dose methylprednisolone for veno-occlusive disease of the liver in pediatric hematopoietic stem cell transplantation recipients. *Biology of Blood and Marrow Transplantation* 2013;**19**:500-3.

Nagasue 1979 *{published data only}*

Nagasue N, Inokuchi K. Spontaneous and traumatic rupture of hepatoma. *British Journal of Surgery* 1979;**66**:248-50.

Nagatoshi 1997 *{published data only}*

Nagatoshi Y, Okamura J, Ikuno Y, Akamatsu M, Tasaka H. Therapeutic trial of intensified conditioning regimen with high-dose cytosine arabinoside, cyclophosphamide and either total body irradiation or busulfan followed by allogeneic bone marrow transplantation for myelodysplastic syndrome in children. *International Journal of Hematology* 1997;**65**:269-75.

Neilson 1996 *{published data only}*

Neilson J, Harrison P, Milligan DW, Skidmore SJ, Collingham KE. Hepatitis G virus in long-term survivors of haematological malignancy. *Lancet* 1996;**347**:1632-3.

Nottage 2013 *{published data only}*

Nottage K, Gurney JG, Smeltzer M, Castellanos M, Hudson MM, Hankins JS. Trends in transfusion burden among long-term survivors of childhood hematological malignancies. *Leukemia and Lymphoma* 2013;**54**:1719–23.

O'Hara 1968 *{published data only}*

O'Hara JM, Hutter RV, Foote FW Jr, Miller T, Woodard HQ. An analysis of thirty patients surviving longer than ten years after treatment for osteogenic sarcoma. *Journal of Bone and Joint Surgery. American Volume* 1968;**50**:335-54.

Oeffinger 2006 *{published data only}*

Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. *New England Journal of Medicine* 2006;**355**:1572-82.

Orchard 2015 *{published data only}*

Orchard PJ, Fasth AL, Le Rademacher J, He W, Boelens JJ, Horwitz EM, et al. Hematopoietic stem cell transplantation for infantile osteopetrosis. *Blood* 2015;**126**:270-6.

Osborne 1980 *{published data only}*

Osborne CK, Norton L, Young RC, Garvin AJ, Simon RM, Berard CW, et al. Nodular histiocytic lymphoma: an aggressive nodular lymphoma with potential for prolonged disease-free survival. *Blood* 1980;**56**:98-103.

Oue 2015 *{published data only}*

Oue T, Miyoshi Y, Hashii Y, Uehara S, Ueno T, Nara K, et al. Problems during the long-term follow-up after surgery for pediatric solid malignancies. *European Journal of Pediatric Surgery* 2015;**25**:123-7.

Ozawa 2017 *{published data only}*

Ozawa M, Ishida Y, Kobayashi K, Nagase K, Gunzi M, Maeda K, et al. The feasibility of a comprehensive medical check-up in adolescent and young adult survivors of childhood cancer. *Pediatric Blood and Cancer* 2017;**64 (Supplement 4)**:S101.

Pantoja 1975 *{published data only}*

Pantoja E, Rodriguez-Ibanez I, Axtmayer RW, Noy MA, Pelegrina I. Complications of dermoid tumors of the ovary. *Obstetrics and Gynecology* 1975;**45**:89-94.

Pao 1989 *{published data only}*

Pao WJ, Hustu HO, Douglass EC, Beckford NS, Kun LE. Pediatric nasopharyngeal carcinoma: long term follow-up of 29 patients. *International Journal of Radiation Oncology, Biology, Physics* 1989;**17**:299-305.

Park 2002 *{published data only}*

Park SH, Lee MH, Lee H, Kim HS, Kim K, Kim WS, et al. A randomized trial of heparin plus ursodiol vs heparin alone to prevent hepatic veno-occlusive disease after hematopoietic stem cell transplantation. *Bone Marrow Transplantation* 2002;**29**:137-43.

Perwein 2011 *{published data only}*

Perwein T, Lackner H, Sovinz P, Benesh M, Schmidt S, Schwinger W, et al. Survival and late effects in children with stage 4 neuroblastoma. *Pediatric Blood and Cancer* 2011;**57**:629-35.

Poussin-Rosillo 1976 *{published data only}*

Poussin-Rosillo H, Nisce LZ, D'Angio GJ. Hepatic radiation tolerance in Hodgkins disease patients. *Radiology* 1976;**121**:461-4.

Pratt 1977 *{published data only}*

Pratt C, Shanks E, Hustu O, Rivera G, Smith J, Kumar AP. Adjuvant multiple drug chemotherapy for osteosarcoma of the extremity. *Cancer* 1977;**39**:51-7.

Pritchard 2005 *{published data only}*

Pritchard J, Cotterill SJ, Germond SM, Imeson J, De Kraker J, Jones DR. High dose melphalan in the treatment of advanced neuroblastoma: results of a randomised trial (ENSG-1) by the European Neuroblastoma Study Group. *Pediatric Blood and Cancer* 2005;**44**:348-57.

Pui 1992 *{published data only}*

Pui CH, Simone JV, Hancock ML, Evans WE, Williams DL, Bowman WP, et al. Impact of three methods of treatment intensification on acute lymphoblastic leukemia in children: long-term results of St Jude total therapy study X. *Leukemia* 1992;**6**:150-7.

Punyko 2005 *{published data only}*

Punyko JA, Mertens AC, Gurney JG, Yasui Y, Donaldson SS, Rodeberg DA. Long-term medical effects of childhood and adolescent rhabdomyosarcoma: a report from the childhood cancer survivor study. *Pediatric Blood and Cancer* 2005;**44**:643-53.

Puri 2006 *{published data only}*

Puri DR, Wexler LH, Meyers PA, La Quaglia MP, Healey JH, Wolden SL. The challenging role of radiation therapy for very young children with rhabdomyosarcoma. *International Journal of Radiation Oncology, Biology, Physics* 2006;**65**:1177-84.

Rajendranath 2014 *{published data only}*

Rajendranath R, Veeraiah S, Ramesh A, Sagar T. Late effects of treatment in survivors of childhood cancer from a tertiary cancer center in South India. *South Asian Journal of Cancer* 2014;**3**:60-5.

Ravikumara 2006 *{published data only}*

Ravikumara M, Hill FGH, Wilson DC, Gillet PM, Thomas A, Brown R, et al. 6-Thioguanine-related chronic hepatoxicity and variceal haemorrhage in children treated for acute lymphoblastic leukaemia - a dual-centre experience. *Journal of Pediatric Gastroenterology and Nutrition* 2006;**42**:535-8.

Reaman 1985 *{published data only}*

Reaman G, Zeltzer P, Bleyer WA. Acute lymphoblastic leukemia in infants less than one year of age: a cumulative experience of the Childrens Cancer Study Group. *Journal of Clinical Oncology* 1985;**3**:1513-21.

Rodriguez-Inigo 1997 *{published data only}*

Rodriguez-Inigo E, Tomás JF, Gómez-García de Soria V, Bartolomé J, Pinilla I, Amaro MJ, et al. Hepatitis C and G virus infection and liver dysfunction after allogeneic bone marrow: results from a prospective study. *Blood* 1997;**90**:1326-31.

Rossetti 1992 *{published data only}*

Rossetti F, Cesaro S, Pizzocchero P, Cadrobbi P, Guido M, Zanesco L. Chronic hepatitis B surface antigen-negative hepatitis after treatment of malignancy. *Journal of Pediatrics* 1992;**121**:39-43.

Ruccione 2012 *{published data only}*

Ruccione KS, Mudambi K, Sposto R, Fridey J, Ghazarossian S, Freyer DR. Association of projected transfusional iron burden with treatment intensity in childhood cancer survivors. *Pediatric Blood and Cancer* 2012;**59**:697–702.

Ruccione 2014 *{published data only}*

Ruccione KS, Wood JC, Sposto R, Malvar J, Chen C, Freyer DR. Characterization of transfusion-derived iron deposition in childhood cancer survivors. *Cancer Epidemiology Biomarkers and Prevention* 2014;**23**(9):1913-9.

Samuelsson 1999 *{published data only}*

Samuelsson BO, Ridell B, Rockert L, Gustafsson G, Marky I. Non-Hodgkin lymphoma in children: a 20-year population-based epidemiologic study in western Sweden. *Journal of Pediatric Hematology/Oncology* 1999;**21**:103-10.

Sawamura 1998 *{published data only}*

Sawamura Y, Ikeda J, Shirato H, Tada M, Abe H. Germ cell tumours of the central nervous system: treatment consideration based on 111 cases and their long-term clinical outcomes. *European Journal of Cancer* 1998;**34**:104-10.

Schaison 1980 *{published data only}*

Schaison G, Jacquillat C, Lemercier N, Weil M, Alby N, Auclerc MF, et al. Acute leukemia in childhood: present status of 100 cases after 7 years of complete remission [Leucémië aigu. Bilan de 100 enfents en rémission plus 7 ans]. *Bulletin du Cancer* 1980;**67**:261-8.

Schmidt 2010 *{published data only}*

Schmidt D, Anderson L, Bingen K, Hoag J, Kupst MJ, Warwick AB. Late effects in adult survivors of childhood cancer: considerations for the general practitioner. *Wisconsin Medical Journal* 2010;**109**:98-108.

Scordo 2017 *{published data only}*

Scordo M, Shah GL, Kosuri S, Herrera DA, Cho C, Devlin SM, et al. Post-transplant toxicities and outcomes in long-term survivors of Ex-Vivo CD34+ selected allogeneic hematopoietic cell transplantation. *Biology of Blood and Marrow Transplantation* 2017;**23 (3 Supplement 1)**:S199-200.

Scordo 2018 *{published data only}*

Scordo M, Shah GL, Kosuri S, Herrera DA, Cho C, Devlin SM, et al. Effects of late toxicities on outcomes in long-term survivors of ex-vivo CD34(+)-selected allogeneic hematopoietic cell transplantation. *Biology of Blood and Marrow Transplantation* 2018;**24**:133-41.

Sekine 1998 *{published data only}*

Sekine I, Dobashi H, Kogawa K, Hirota T, Katano N, Kawakami K, et al. Hepatitis C virus infection and chronic liver diseases after treatment of malignant disease in children: a multicenter study from the Children's Cancer and Leukemia Study Group of Japan. *International Journal of Clinical Oncology* 1998;**3**:247-52.

Sevinir 2003 *{published data only}*

Sevinir B, Meral A, Günay Ü, Özkan T, Özuysal S, Sinirtas M. Increased risk of chronic hepatitis in children with cancer. *Medical and Pediatric Oncology* 2003;**40**:104-10.

Shah 2004 *{published data only}*

Shah AJ, Lenarsky C, Kapoor N, Crooks GM, Kohn DB, Parkman R. Busulfan and cyclophosphamide as a conditioning regimen for pediatric acute lymphoblastic leukemia patients undergoing bone marrow transplantation. *Journal of Pediatric Hematology/Oncology* 2004;**26**:91-7.

Silverman 1997 *{published data only}*

Silverman LB, McLean TW, Gelber RD, Donnelly MJ, Gary GD, Tarbell NJ, et al. Intensified therapy for infants with acute lymphoblastic leukemia: results from the Dana-Farber Cancer Institute Consortium. *Cancer* 1997;**80**:2285-95.

Sirvent 2017 *{published data only}*

Sirvent A, Auquier P, Oudin C, Bertrand Y, Bohrer S, Chastagner P, et al. Prevalence and risk factors of iron overload after hematopoietic stem cell transplantation for childhood acute leukemia: a LEA study. *Bone Marrow Transplantation* 2017;**52**:80-7.

Sivaprakasan 2011 *{published data only}*

Sivaprakasam P, Gupta AA, Greenberg ML, Capra M, Nathan PC. Survival and long-term outcomes in children with hepatoblastoma treated with continuous infusion of cisplatin and doxorubicin. *Journal of Pediatric Hematology and Oncology* 2011;**33**:e226-e230.

Skidmore 1997 *{published data only}*

Skidmore SJ, Collingham KE, Harrison P, Neilson JR, Pillay D, Milligan DW. High prevalence of hepatitis G virus in bone marrow transplant recipients and patients treated for leukemia.. *Blood* 1997;**89**:3853-6.

Skinner 2012 *{published data only}*

Skinner R. Long-term effects of cancer therapy in children - organs, systems and tissues. *Paediatrics and Child Health* 2012;**22**:201-6.

Smith 2012 *{published data only}*

Smith EA, Salisbury S, Martin R, Towbin AJ. Incidence and etiology of new liver lesions in pediatric patients previously treated for malignancy. *American Journal of Roentgenology* 2012;**199**:186-91.

Socié 1999 *{published data only}*

Socié G, Stone JV, Wingard JR, Weisdorf D, Henslee-Downey PJ, Bredeson C, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. *New England Journal of Medicine* 1999;**341**:14-21.

Socié 2001 *{published data only}*

Socié G, Clift RA, Blaise D, Devergie A, Ringden O, Martin PJ, et al. Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow-up of 4 randomized studies. *Blood* 2001;**98**:3569-74.

Spunberg 1981 *{published data only}*

Spunberg JJ, Chang CH, Goldman M. Quality of long-term survival following irradiation for intracranial tumors in children under the age of two. *International Journal of Radiation Oncology, Biology, Physics* 1981;**7**:727-36.

Strasser 1999a *{published data only}*

Strasser SI, Sullivan KM, Myerson D, Spurgeon CL, Storer B, Schoch HG, et al. Cirrhosis of the liver in long-term marrow transplant survivors. *Blood* 1999;**93**:3259-66.

Strasser 1999b *{published data only}*

Strasser SI, Myerson D, Spurgeon CL, Sullivan KM, Storer B, Schoch HG, et al. Hepatitis C virus infection and bone marrow transplantation: a cohort study with 10-year-follow-up. *Hepatology* 1999;**29**:1893-9.

Straus 1991 *{published data only}*

Straus DJ, Wong G, Yahalom J, Varsos G, Gulati S, Clarkson B. Diffuse large cell lymphoma. Prognostic factors with treatment. *Leukemia* 1991;**5 Suppl 1**:32-7.

Sudour 2009 *{published data only}*

Sudour H, Mainard L, Baumann C, Clement L, Salmon A, Bordigoni P. Focal nodular hyperplasia of the liver following hematopoietic SCT. *Bone Marrow Transplantation* 2009;**43**:127–32.

Tada 1997 *{published data only}*

Tada K, Tajiri H, Kozaiwa K, Sawada A, Guo W, Okada S. Role of screening for hepatitis C virus in children with malignant disease who undergo bone marrow transplantation. *Transfusion* 1997;**37**:641-4.

Takeishi 2015 *{published data only}*

Takeishi K, Maeda T, Shirabe K, Tsujita E, Yamashita Y, Harimoto N, et al. Clinicopathologic features and outcomes of non-B, non-C hepatocellular carcinoma after hepatectomy. *Annals of Surgical Oncology* 2015;**22 (Suppl 3)**:S1116-24.

Taylor 1997 *{published data only}*

Taylor RE. Morbidity from abdominal radiotherapy in the first United Kingdom Children's Cancer Study Group Wilms' Tumour Study. *Clinical Oncology* 1997;**9**:381-4.

Tefft 1977 *{published data only}*

Tefft M. Radiation related toxicities in National Wilms' Tumor Study Number 1. *International Journal of Radiation Oncology, Biology, Physics* 1977;**2**:455-63.

Thomas 1988 *{published data only}*

Thomas PR, Tefft M, D'Angio GJ, Norkool P. Acute toxicities associated with radiation in the second National Wilms' Tumor Study. *Journal of Clinical Oncology* 1988;**6**:1694-8.

Tomás 2000 *{published data only}*

Tomás JF, Pinilla I, García-Buey ML, García A, Figuera A, Gómez-García de Soria V, et al. Long-term liver dysfunction after allogeneic bone marrow transplantation: clinical features and course in 61 patients. *Bone Marrow Transplantation* 2000;**26**:649-55.

Trovillion 2018 *{published data only}*

Trovillion EM, Schubert L, Dietz AC. Iron overload in survivors of childhood cancer. *Journal of Pediatric Hematology/Oncology* 2018;**40**:396-400.

Tura 1998 *{published data only}*

Tura S, Rosti G, De Vivo A, Bonifazi F, Fiacchini M, Baccarani M, et al. Long-term follow-up of the Italian trial of interferon-alpha versus conventional chemotherapy in chronic myeloid leukemia. *Blood* 1998;**92**:1541-8.

Uchino 1978 *{published data only}*

Uchino J, Hata Y, Kasai Y. Stage IVS neuroblastoma. *Journal of Pediatric Surgery* 1978;**13**:167-72.

Uzel 2001 *{published data only}*

Uzel O, Yoruk SO, Sahinler I, Turkan S, Okkan S. Nasopharyngeal carcinoma in childhood: long-term results of 32 patients. *Radiotherapy and Oncology* 2001;**58**:137-41.

Vaidya 2000 *{published data only}*

Vaidya S, Atra A, Bahl S, Pinkerton CR, Calvagna V, Horton C, et al. Autologous bone marrow transplantation for childhood acute lymphoblastic leukaemia in second remission - long-term follow-up. *Bone Marrow Transplantation* 2000;**25**:599-603.

Van den Ouweland 1983 *{published data only}*

Van den Ouweland FA, Holdrinet RSG, De Pauw BE, Haanen O. Transaminase, hepatitis B, and prognosis in acute nonlymphoblastic leukemia. *New England Journal of Medicine* 1983;**309**:990.

Van Dijk 2010 *{published data only}*

Van Dijk IWEM, Oldenburger F, Cardous-Ubbink MC, Geenen MM, Heinen RC, De Kraker J, et al. Evaluation of late adverse events in long-term Wilms' tumor survivors. *International Journal of Radiation Oncology Biology Physics* 2010;**78**:370-8.

Veneri 2003 *{published data only}*

Veneri D, Franchini M, Zanetti F, Krampera M, De Matteis G, Pizzolo G. Iron overload in acute myeloid leukemia patients is not related to HFE and TFR2 gene mutations. *Haematologica* 2003;**88**:1069-70.

Vergani 1982 *{published data only}*

Vergani D, Locasciulli A, Masera G, Alberti A, Moroni G, Tee DEH, et al. Histologic evidence of hepatitis-B-virus infection with negative serology in children with acute leukemia who develop chronic liver disease. *Lancet* 1982;**13**:361-4.

Von Schweinitz 1994 *{published data only}*

Von Schweinitz D, Bürger D, Bode U, Weinel P, Erttmann R, Hecker H, et al. Results of the HB-89 study in treatment of malignant epithelial liver tumors in childhood and concept of a new HB-94 protocol [Ergebnisse der studie HB-89 bei behandlung maligner epithelialer lebertumoren des kindesalters und konzept eines neuen protokolls HB-94]. *Klinische Pädiatrie* 1994;**206**:282-8.

Wasserheit 1995 *{published data only}*

Wasserheit C, Acaba L, Gulati S. Abnormal liver function in patients undergoing autologous bone marrow transplantation for hematological malignancies. *Cancer Investigation* 1995;**13**:347-54.

Weirich 2004 *{published data only}*

Weirich A, Ludwig R, Graf N, Abel U, Leuschner I, Vujanic GM, et al. Survival in nephroblastoma treated according to the trial and study SIOP-9/GPOH with respect to relapse and morbidity. *Annals of Oncology* 2004;**15**:808-20.

Wexler 1996 *{published data only}*

Wexler LH, Andrich MP, Venzon D, Berg SL, Weaver-McClure L, Chen CC, et al. Randomized trial of the cardioprotective agent ICRF-187 in pediatric sarcoma patients treated with doxorubicin. *Journal of Clinical Oncology* 1996;**14**:362-72.

Willers 2001 *{published data only}*

Willers E, Webber L, Delport R, Kruger M. Hepatitis B - a major threat to childhood survivors of leukaemia/lymphoma. *Journal of Tropical Pediatrics* 2001;**47**:220-5.

Wolff 2006 *{published data only}*

Wolff JEA, Wagner S, Reinert C, Gnekow A, Kortmann RD, Kuhl J, et al. Maintenance treatment with interferon-gamma and low-dose cyclophosphamide for pediatric high-grade glioma. *Journal of Neuro-Oncology* 2006;**79**:315-21.

Woolfrey 1998 *{published data only}*

Woolfrey AE, Gooley TA, Sievers EL, Milner LA, Andrews RG, Walters M, et al. Bone marrow transplantation for children less than 2 years of age with acute myelogenous leukemia or myelodysplastic syndrome. *Blood* 1998;**92**:3546-56.

Yamada-Osaki 1999 *{published data only}*

Yamada-Osaki M, Sumazaki R, Tsuchida M, Koike K, Fukushima T, Matsui A. Persistence and clinical outcome of hepatitis G virus infection in pediatric bone marrow transplant recipients and children treated for hematological malignancy. *Blood* 1999;**93**:721-7.

Yang 2005 *{published data only}*

Yang CP, Hung IJ, Jaing TH, Shih LY, Chang WH. Cancer in infants: a review of 82 cases. *Pediatric Hematology and Oncology* 2005;**22**:463-81.

Yang 2006 *{published data only}*

Yang CP, Hung IJ, Jaing TH, Chang WH. Cancers in the infancy: percent distribution and incidence rates. *Acta Paediatrica Taiwanica* 2006;**47**:273-7.

Yock 2016 *{published data only}*

Yock TI, Yeap BY, Ebb DH, Weyman E, Eaton BR, Sherry NA, et al. Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study. *Lancet Oncology* 2016;**17**:287-98.

Yoo 2013 *{published data only}*

Yoo SY, Kim JH, Eo H, Jeon TY, Sung KW, Kim HS. Dynamic MRI findings and clinical features of benign hypervascular hepatic nodules in childhood-cancer survivors. *American Journal of Roentgenology* 2013;**201**:178-84.

Zhou 2009 *{published data only}*

Zhou XD, Tang ZY, Ma ZC, Fan J, Wu ZQ, Qin LX, et al. Twenty-year survivors after resection for hepatocellular carcinoma - analysis of 53 cases. *Journal of Cancer Research and Clinical Oncology* 2009;**135**:1067-72.

Zimmermann 2002 *{published data only}*

Zimmermann SY, Klingebiel T, Koehl U, Soerensen J, Schwabe D. Tecelac as antihymocyte globulin in conditioning for childhood allogeneic stem cell transplantation. *Bone Marrow Transplantation* 2002;**29**:957-62.

Zittoun 1985 *{published data only}*

Zittoun R, Rio B, Marie JP, Blanc CM. AMSA combined with high dose cytosine-arabinoside in acute leukaemia. *Presse Medicale* 1985;**14**:1417-20.

References to studies awaiting assessment

Halley 2012 *{published data only}*

Halley N, Cristofani LM, Almeida MTA, Maluf-Junior PT, Cornacchioni ALB, Teixeira RAP, et al. Long term complications in children treated for advanced neuroblastoma. *Pediatric Blood and Cancer* 2012;**59**:1060 [abstract PH033].

Kovacs 2007 *{published data only}*

Kovacs G, Sapi C, Csoka M, Erdelyi D, Haltrich I, Muller J. Hepatotoxic late side effects in children with haematological malignancies. *Pediatric Blood and Cancer* 2007;**49**:547-8 [abstract PL.004].

Kristinsson 2002 *{published data only}*

Kristinsson VH, Kristinsson JR, Jonmundsson GK, Jonsson OG, Porsson AV, Haraldsson A. Late and long-term effects of leukemia treatment in childhood [Siokmnar of langvinnar aukaverkanir eftir hvitblaeoismeofero i aesku]. *Laeknabladid* 2002;**88**:13-8.

Lee 2014 *{published data only}*

Lee YH, Shin H, Kang H, Yang S. Prevalence and monitoring of components of the metabolic syndrome in adolescent survivors of childhood cancer. *Pediatric Blood and Cancer* 2014;**61**:S307 [abstract EP-238].

Meneghello 2016 *{published data only}*

Meneghello L, Alaggio R, Dall'Igna P, Paratella A, Cecchetto G, Bisogno G. Clinical and histological correlation of hepatic veno-occlusive. *Pediatric Blood and Cancer* 2016;**63**:S246-247 [abstract P-0760].

Thavaraj 2006 *{published data only}*

Thavaraj V, Seth R, Arya LS, Kumar R. Screening for problems of pediatric cancer survivors in our center. *Pediatric Blood and Cancer* 2006;**47**:481 [abstract PJ.032].

Additional references

Baldo 2008

Baldo V, Baldovin T, Trivello R, Floreani A. Epidemiology of HCV infection. *Current Pharmaceutical Design* 2008;**14**:1646-54.

Castellino 2004

Castellino S, Lensing S, Riely C, Rai SN, Davila R, Hayden RT, et al. The epidemiology of chronic hepatitis C infection in survivors of childhood cancer: an update of the St Jude Children's Research Hospital hepatitis C seropositive cohort. *Blood* 2004;**103**:2460-6.

Curry 2006

Curry HL, Parkes SE, Powell JE, Mann JR. Caring for survivors of childhood cancer: the size of the problem. *European Journal of Cancer* 2006;**42**:501-8.

Dawson 2005

Dawson LA, Ten Haken RK. Partial volume tolerance of the liver to radiation. *Seminars in Radiation Oncology* 2005;**15**:279-83.

Field 2008

Field KM, Dow C, Michael M. Part I: Liver function in oncology: biochemistry and beyond. *Lancet* 2008;**9**:1092-101.

Gatta 2009

Gatta G, Zigon G, Capocaccia R, Coebergh JW, Desandes E, Kaatsch P, et al. Survival of European children and young adults with cancer diagnosed between 1995-2002. *European Journal of Cancer* 2009;**45**:992-1005.

Geenen 2007

Geenen MM, Cardous-Ubbink MC, Kremer LCM, Van den Bos C, Van der Pal HJH, Heinen RC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA* 2007;**297**:2705-15.

Grimes 2002

Grimes DA, Schultz KF. Cohort studies: marching towards outcomes. *Lancet* 2002;**359**:341-5.

Higgins 2011

Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hudson 2005

Hudson MM. Late gastrointestinal and hepatic effects. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS editor(s). Survivors of Childhood and Adolescent Cancer. A Multidisciplinary Approach. Second Edition. New York: Springer, 2005:181-202.

Kim 2008

Kim WR, Flamm SL, Di Bisceglie AMD, Bodenheimer HC, Public Policy Committee of the American Association for the Study of Liver Disease. Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease. *Hepatology* 2008;**47**:1363-70.

King 2001

King PD, Perry MC. Hepatotoxicity of chemotherapy. *Oncologist* 2001;**6**:162-76.

Kurbegov 2009

Kurbegov AC, Sokol RJ. Hepatitis B therapy in children. *Expert Review of Gasteroenterology & Hepatology* 2009;**3**:39-49.

Laupacis 1994

Laupacis A, Wells G, Richardson WS, Tugwell P, Evidence-Based Working Group. Users' guides to the medical literature. V. How to use an article about prognosis. *JAMA* 1994;**272**:234-7.

Leung 2007

Leung W, Ahn H, Rose SR, Phipps S, Smith T, Gan K, et al. A prospective cohort study of late sequelae of pediatric allogeneic hematopoietic stem cell transplantation. *Medicine* 2007;**86**:215-24.

Locasciulli 1997

Locasciulli A, Testa M, Valsecchi MG, Vecchi I, Longoni D, Sparano P, et al. Morbidity and mortality due to liver disease in children undergoing allogeneic bone marrow transplantation: a 10-year prospective study. *Blood* 1997;**90**:3799-805.

Luyckx 2000

Luyckx FH, Lefebvre PJ, Scheen AJ. Non-alcoholic steatohepatitis: association with obesity and insulin resistance, and influence of weight loss. *Diabetes and Metabolism* 2000;**26**:98–106.

Maddrey 2000

Maddrey WC. Alcohol-induced liver disease. *Clinics in Liver Disease* 2000;**4**:115–31.

Meacham 2005

Meacham LR1, Gurney JG, Mertens AC, Ness KK, Sklar CA, Robison LL, et al. Body mass index in long-term adult survivors of childhood cancer: a report of the Childhood Cancer Survivor Study. *Cancer* 2005;**103**:1730-9.

Meacham 2010

Meacham LR, Chow EJ, Ness KK, Kamdar KY, Chen Y, Yasui Y, et al. Cardiovascular risk factors in adult survivors of pediatric cancer - a report from the Childhood Cancer Survivor Study. *Cancer Epidemiology Biomarkers and Prevention* 2010;**19**:170-81.

Rizzo 2006

Rizzo JD, Wingard JR, Tichelli A, Lee SJ, Van Lint MT, Burns LJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, and the American Society of Blood and Marrow Transplantation. *Biology of Blood and Marrow Transplantation* 2006;**12**:138-51.

Ruhl 2009

Ruhl CE, Everhart JE. Elevated serum alanine aminotransferase and gamma-glutamyltransferase and mortality in the United States population. *Gastroenterology* 2009;**136**:477-85.

Saleh 2007

Saleh HA, Abu-Rashed AH. Liver biopsy remains the gold standard for evaluation of chronic hepatitis and fibrosis. *Journal of Gastrointestinal and Liver Diseases* 2007;**16**:425-6.

Sheen 2002

Scheen AJ, Luyckx FH. Obesity and liver disease. *Best Practice and Research. Clinical Endocrinology and Metabolism* 2002;**16**:703-16.

Strasser 1999

Strasser SI, Sullivan KM, Myerson D, Spurgeon CL, Storer B, Schoch HG, et al. Cirrhosis of the liver in long-term marrow transplant survivors. *Blood* 1999;**93**:3259-66.

Strickland 2000

Strickland DK, Riely CA, Patrick CC, Jones-Wallace D, Boyett JM, Waters B, et al. Hepatitis C infection among survivors of childhood cancer. *Blood* 2000;**95**:3065-70.

Villano 1999

Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. *Hepatology* 1999;**29**:908-14.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aricò 1994

Methods	Cohort study
Participants	*N* of participants original cohort: 102 *N* of participants described study group: 102 *N* of participants study group of interest: 102 *N* of participants with liver function tests: 102 Tumour: ALL Time period diagnosis/treatment: 1977-1992 Age at diagnosis: nm Age at follow-up: median 10.5 (2.5 to 21.1) yr F/M%: 45/55 BMI: nm *N* of participants hepatitis virus infection: 23/102 (22.5%) HCV-RNA^{+} (persistent HCV) and 7/102 (6.8%) anti-HCV^{+}, HCV-RNA^{-} *N* of participants acute liver disease: nm Follow-up duration: median 2.8 (0.1 to 12.5) yr after end of treatment Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: 102/102 (100%); chemotherapy type: nm; chemotherapy dose: nm

References to other published versions of this review

Mulder 2010

Mulder RL, Van Dalen EC, Bresters D, Loke Y, Leclercq E, Postma A, et al. Hepatic late adverse effects after treatment for childhood cancer. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD008205]

Mulder 2011

Mulder RL, Van Dalen EC, Van den Hof M, Bresters D, Koot BGP, Castellino SM, et al. Hepatic late adverse effects after antineoplastic treatment for childhood cancer. *Cochrane Database of Systematic Reviews* 2011, Issue 7. [DOI: 10.1002/14651858.CD008205]

Review Manager 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Aricò 1994 *(Continued)*

	N of participants radiotherapy involving the liver: nm; radiotherapy field: nm; radiotherapy dose: nm
	N of participants hepatectomy: nm
	N of participants BMT: nm
	N of participants blood transfusion: 101/102 (99.0%)
Outcomes	Method of detection of hepatic late adverse effects: ALT (frequency of testing nm)
	Definition of hepatic late adverse effects: ALT > upper limit of normal (35 IU/mL)
	N of participants hepatic late adverse effects at end of follow-up: 22/102 (21.6%) of whom 5/102 (4.9%) had mild-to-moderate increase, 16/102 (15.7%) moderate increase and 1/102 (1.0%) severe increase (> 3.5 times upper limit of normal (35 IU/mL))
	Risk factors: chronic HCV infection: 16/23 (69.6%) with chronic HCV infection elevated ALT versus 6/79 (7.6%) without chronic HCV infection elevated ALT (P < 0.001) (univariable)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Low risk	Described study group consisted of more than 90% of the original cohort
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	High risk	Type of chemotherapy was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise
Well defined risk estimation	Low risk	Chi^2 was calculated

Ballauff 1999

Methods	Prospective cohort study
Participants	*N* of participants original cohort: 50
	N of participants described study group: 50
	N of participants study group of interest: 50
	N of participants with liver function tests: 50
	Tumour: various tumours; time period diagnosis/treatment: 1980-1991

Ballauff 1999 *(Continued)*

	Age at diagnosis: nm Age at follow-up: median 12.3 (6.7 to 24.5) yr F/M%: 36/64 BMI: nm *N* of participants hepatitis virus infection: 14/50 (28.0%) HCV-RNA$^+$ (persistent HCV), 2/50 (4.0%) anti-HCV$^+$ and HCV-RNA$^-$, and 2/50 (4.0%) HBsAntigen$^+$ *N* of participants acute liver disease: 43/50 (86.0%) elevated AST/ALT during chemotherapy; 13/50 (26.0%) elevated bilirubin and γGT during chemotherapy Follow-up duration: median 3.6 (0.5 to 11.8) yr after end of treatment Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: 50/50 (100%); chemotherapy type: nm; chemotherapy dose: nm *N* of participants radiotherapy involving the liver: nm; radiotherapy field: nm; radiotherapy dose: nm *N* of participants hepatectomy: nm *N* of participants BMT: nm *N* of participants blood transfusion: 50/50 (100%)
Outcomes	Method of detection of hepatic late adverse effects: ALT, AST, bilirubin, γGT (frequency of testing nm) Definition of hepatic late adverse effects: ALT > upper limit of normal (24 U/L), AST > upper limit of normal (22 U/L), bilirubin > 1.5 mg/dL (normal: 0.3 mg/dL), γGT > 100 U/L (normal: 20 U/L) *N* of participants hepatic late adverse effects at end of follow-up: 16/50 (32.0%) Risk factors: chronic HBV/HCV infection: 13/16 (81.3%) with abnormal liver function tests chronic HBV/HCV infection versus 2/34 (5.9%) with normal liver function tests chronic HBV/HCV infection (P = 0.001) (univariable)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Low risk	Described study group consisted of more than 90% of the original cohort
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	High risk	Type of chemotherapy was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned

Ballauff 1999 *(Continued)*

Well defined outcome	Low risk	Outcome definition was objective and precise
Well defined risk estimation	Low risk	Chi^2 was calculated

Bessho 1994

Methods	Cohort study
Participants	*N* of participants original cohort: nm *N* of participants described study group: 25 *N* of participants study group of interest: 25 *N* of participants with liver function tests: 25 Tumour: ALL Time period diagnosis/treatment: nm Age at diagnosis: median 4.4 (1.2 to 15.0) yr Age at follow-up: median 15.0 (6.8 to 22.0) yr F/M%: 41/59 BMI: nm *N* of participants hepatitis virus infection: 0/23 (0.0%) anti-HCV^+ and 0/23 (0.0%) $HBsAntigen^+$ *N* of participants acute liver disease: 24/25 (96.0%) elevated ALT during chemotherapy and 20/25 (80.0%) elevated ALT at end chemotherapy Follow-up duration: median 4.2 (1.0 to 7.5) yr after end of treatment Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: 25/25 (100%); chemotherapy type: prednisolone, vincristine, daunorubicin, L-asparaginase, methotrexate and 6-mercaptopurine; chemotherapy dose: induction therapy consisted of daily prednisolone 60 mg/m^2 for 4 weeks, 5 doses of weekly vincristine 1.5 mg/m^2, 5 doses of weekly daunorubicin 25 mg/m^2 and 4 doses of weekly L-asparaginase 10,000 U/m^2 or 8 doses of biweekly L-asparaginase 6000 U/m^2. Prophylaxis of central nervous system leukaemia consisted of 5 doses weekly methotrexate 12 mg/m^2. Maintenance therapy consisted of daily 6-mercaptopurine and weekly methotrexate. Initial doses of methotrexate and 6-mercaptopurine were 20 mg/m^2 and 50 mg/m^2, respectively. Mean methotrexate dose actually administered: 3.35 ± 1.27 g/m^2. Mean 6-mercaptopurine dose actually administered: 59.65 ± 21.16 g/m^2 *N* of participants radiotherapy involving the liver: nm; radiotherapy field: nm; radiotherapy dose: nm *N* of participants hepatectomy: nm *N* of participants BMT: nm *N* of participants blood transfusion: 23/25 (92.0%)
Outcomes	Method of detection of hepatic late adverse effects: ALT, bilirubin, albumin, PTT (measured 3-12 monthly 1 yr after the end of treatment) Definition of hepatic late adverse effects: ALT > upper limit of normal (33.3 IU/L); bilirubin, albumin, PTT: nm *N* of participants hepatic late adverse effects at end of follow-up: ALT: 2/25 (8.0%); bilirubin, albumin and PTT: 0/25 (0.0%) Risk factors: not evaluated

Bessho 1994 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Well defined study group	Low risk	Type of chemotherapy and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

Bresters 2008

Methods	Retrospective cohort study
Participants	*N* of participants original cohort: 290 *N* of participants described study group: 216 *N* of participants study group of interest: 216 *N* of participants with liver function tests: 216 Tumour: haematological malignancy: ALL, AML, CML, JMML, MDS, lymphoma (n = 129), benign haematological disease (n = 54), immunological disease (n = 22), other inborn errors (n = 11) Time period diagnosis/treatment: 1980-2002 Age at diagnosis: nm (age at HSCT: median 7.6 (0.1 to 18.4) yr) Age at follow-up: nm F/M%: 40/60 BMI: nm *N* of participants hepatitis virus infection: 3/139 (2.1%) anti-HCV$^+$ and 0/183 (0.0%) HBsAntigen$^+$ *N* of participants acute liver disease: 14/216 (6.5%) SOS and 5/216 (2.3%) acute GVHD Follow-up duration: 2 yr after HSCT, plus or minus 6 months Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: 211/216 (97.7%); chemotherapy type: cyclophosphamide (n = 121), cyclophosphamide with busulphan (n = 69), other unspecified (n = 21); chemotherapy dose: nm

Bresters 2008 *(Continued)*

	N of participants radiotherapy involving the liver: 132/216 (61.1%); radiotherapy field: TBI/TAI; radiotherapy dose: nm *N* of participants hepatectomy: nm *N* of participants BMT: 216/216 (100%) *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT, AST (frequency of testing nm) Definition of hepatic late adverse effects: ALT and/or AST > upper limit of normal (mean plus 2 standard deviations as determined in a normal Dutch population) *N* of participants hepatic late adverse effects at end of follow-up: 53/216 (24.5%) of whom 17/216 (7.9%) had ALT/AST ≥ 2 times upper limit of normal. In 12/13 (92.3%) participants with ALT/AST ≥ 2 times upper limit of normal persisting abnormal liver enzymes 3 years after HSCT. Risk factors: Older age at HSCT: median age 9.9 yr in participants with elevated ALT/AST versus 7.2 yr in participants with normal ALT/AST (P = 0.027); diagnosis of benign haematological disease (OR, 2.59; 95% CI, 1.32 to 5.05) (P = 0.005); gender, donor type (matched sibling donor, other), stem cell source (bone marrow, autologous peripheral blood, cord blood), conditioning regimen (cyclophosphamide with TBI/TAI, cyclophosphamide with busulphan, other) and early post-transplant morbidity (viral reactivation after HSCT, SOS, acute GVHD) (ns) (univariable)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	High risk	Described study group consisted of less than 90% of the original cohort and was no random sample of the original cohort with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	Low risk	Type of chemotherapy, location of radiotherapy, and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise
Well defined risk estimation	Low risk	Odds ratio, mean difference and Chi^2 were calculated

Chotsampancharoen 2009

Methods	Prospective cohort study
Participants	*N* of participants original cohort: 205[a]

Chotsampancharoen 2009 *(Continued)*

	N of participants described study group: 133
	N of participants study group of interest: 133
	N of participants with liver function tests: nm
	Tumour: ALL, AML, CML
	Time period diagnosis/treatment: 1990-2005
	Age at diagnosis: nm (age at HSCT: mean 9.1 ± 5.6 (0.6 to 21.4) yr); age at follow-up: nm
	F/M%: 46/54
	BMI: nm
	N of participants hepatitis virus infection: nm
	N of participants acute liver disease: nm
	Follow-up duration: mean 5.6 ± 3.5 (1-15) yr after HSCT
	Completion of follow-up: unclear
Interventions	*N* of participants chemotherapy: nm; chemotherapy type: nm; chemotherapy dose: nm
	N of participants radiotherapy involving the liver: 127/133 (95.5%); radiotherapy field: TBI; radiotherapy dose: 8-14.4 Gy[a]
	N of participants hepatectomy: nm
	N of participants BMT: 133/133 (100%)
	N of participants blood transfusion: 133/133 (100%)
Outcomes	Method of detection of hepatic late adverse effects: ALT, total bilirubin (frequency of testing nm)
	Definition of hepatic late adverse effects: nm
	N of participants hepatic late adverse effects at end of follow-up: nm
	Risk factors: high serum ferritin (iron overload): serum ferritin was positively correlated with ALT (r = 0.17) and total bilirubin (r = 0.21) (P < 0.001) (univariable)
Notes	[a] Reported in Leung 2007

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	High risk	Described study group consisted of less than 90% of the original cohort and was no random sample of the original cohort with respect to cancer treatment
Complete follow-up assessment	Unclear risk	Unclear if outcome was assessed for more than 60% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account

Chotsampancharoen 2009 *(Continued)*

Well defined study group	High risk	Number of participants with hepatitis virus infection was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise
Well defined risk estimation	Low risk	Chi^2 was calculated

Delvecchio 2017

Methods	Cohort study
Participants	*N* of participants original cohort: nm *N* of participants described study group: 53 *N* of participants study group of interest: 53 *N* of participants with liver function tests: 53 *N* of control participants: 34 healthy subjects pair matched by age and sex Tumour: ALL Time period diagnosis/treatment: nm Age at diagnosis: mean 5.4 ± 3.8 yr (inclusion criteria: 4-20 yr) Age at follow-up: mean 9.7 ± 4.1 yr F/M%: 64/36 BMI: standard deviation score 0.9 ± 0.9 *N* of participants hepatitis virus infection: nm *N* of participants acute liver disease: 0 (0%) Follow-up duration: median 28.5 months (range 3 to 102 months) since end of chemotherapy Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: 53 (100%) Chemotherapy type: methotrexate, mercaptopurine, thioguanine, adriamycin, cytarabine, cyclophosphamide, daunorubicin, dexamethasone, asparaginase, prednisone, vincristine Chemotherapy dose: nm *N* of participants radiotherapy involving the liver: 0 (0%) Radiotherapy field: na Radiotherapy dose: na *N* of participants hepatectomy: 0 (0%) *N* of participants BMT: nm *N* of participants blood transfusion: nm

Delvecchio 2017 *(Continued)*

Outcomes	Method of detection of hepatic late adverse effects: ALT, AST and γGT Definition of hepatic late adverse effects: nm *N* of participants hepatic late adverse effects at end of follow-up: mean ALT participants vs controls: 23 ± 6 vs 24 ± 7 IU/mL, P = 0.781, mean AST participants vs controls: 22 ± 6 vs 20 ± 5 IU/mL, P = 0.839; mean γGT participants vs controls: 16 ± 5 vs 18 ± 6 IU/mL, P = 0.690 Risk factors: mean ALT, AST and γGT were not significantly different in participants with ultrasound-negative vs ultrasound-positive steatosis (fatty liver) (P > 0.05) (univariable)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	High risk	Number of participants with hepatitis virus infection was not mentioned
Well defined follow-up	High risk	Exact follow-up duration of the study group was not mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise
Well defined risk estimation	Low risk	ANOVA tests were performed

El-Rashedy 2017

Methods	Cohort study
Participants	*N* of participants original cohort: nm *N* of participants described study group: 35 *N* of participants study group of interest: 35 *N* of participants with liver function tests: 35 *N* of control participants: 35 healthy subjects matched by age and sex Tumour: ALL Time period diagnosis/treatment: nm Age at diagnosis: mean 5.86 ± 1.5 yr (all childhood cancer)

El-Rashedy 2017 *(Continued)*

	Age at follow-up: mean 11.01 ± 4.6 yr F/M%: 40/60 BMI: 13 (37.1%) overweight *N* of participants hepatitis virus infection: 10 (28.6%) anti-HCV$^+$ *N* of participants acute liver disease: nm Follow-up duration: ≥ 5 yr after end of treatment Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: 35 (100%) Chemotherapy type: prednisone, vincristine, daunorubicin, asparaginase, cyclophosphamide, mercaptopurine, cytarabine, high-dose methotrexate Chemotherapy dose: nm (St Jude Total XV Chemotherapy Protocol) *N* of participants radiotherapy involving the liver: 0 (0%) Radiotherapy field: na Radiotherapy dose: na *N* of participants hepatectomy: 0 (0%) *N* of participants BMT: 0 (0%) *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT, AST, total bilirubin, direct bilirubin, serum ferritin Definition of hepatic late adverse effects: nm *N* of participants hepatic late adverse effects at end of follow-up: mean ALT participants vs controls: 51.8 ± 29.67 vs 26 ± 4.81 IU/L, P = 0.03; mean AST participants vs controls: 47.85 ± 27.86 vs 30 ± 4.41 IU/L, P = 0.073; mean total bilirubin participants vs controls: 0.6057 ± 0.235 vs 0.46 ± 0.12 mg/dL, P = 0.036; mean direct bilirubin participants vs controls: 0.18 ± 0.14 vs 0.09 ± 0.05 mg/dL, P = 0.044; mean serum ferritin participants vs controls: 737.6 ± 99.2 vs 51.6 ± 18.2 ng/mL, P = 0.006 Risk factors: mean ALT after low vs standard-dose asparaginase: 22.7 ± 6.7 vs 95.4 ± 47 IU/L, P < 0.001; mean AST after low vs standard-dose asparaginase: 29.9 ± 7.3 vs 74.9 ± 44.1 IU/L, P < 0.001; mean total bilirubin after low vs standard-dose asparaginase: 0.51 ± 0.2 vs 0.74 ± 0.3 mg/dL, P = 0.003; mean direct bilirubin after low vs standard-dose asparaginase: 0.09 ± 0.02 vs 0.14 ± 0.1 IU/L, P = 0.052; no significant correlation between serum ferritin and ALT (r = -0.135, P = 0.44), AST (r = -0.155, P = 0.347), total bilirubin (r = -0.149, P = 0.393) and direct bilirubin (r = 0.027, P = 0.877) (univariable)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest

El-Rashedy 2017 *(Continued)*

Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	Low risk	Type of chemotherapy and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	High risk	Exact follow-up duration of the study group was not mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise
Well defined risk estimation	Low risk	Mann-Whitney test was performed

French 2012

Methods	Retrospective cohort study
Participants	*N* of participants original cohort: 31 *N* of participants described study group: 27 *N* of participants study group of interest: 27 *N* of participants with liver function tests: 23 Tumour: neuroblastoma stage 4S (special) (n = 15; 12 liver involvement; neuroblastoma stage 4 (n = 12; 5 liver involvement) Time period diagnosis/treatment: 1984-2002 Age at diagnosis: median 87 days (2 to 286) days (stage 4S participants); median 176.5 (6 to 297) days (stage 4 participants) Age at follow-up: median 16.7 (5.4 to 19.4) yr F/M%: nm BMI: nm *N* of participants hepatitis virus infection: nm *N* of participants acute liver disease: nm Follow-up duration: range 5.1 to 19.2 yr since diagnosis Completion of follow-up: 85.2%
Interventions	*N* of participants chemotherapy: 27/27 (100%); chemotherapy type: nm; chemotherapy dose: nm *N* of participants radiotherapy involving the liver: 13/27 (48.2%); radiotherapy field: abdomen (n = 12), TBI (n = 1); radiotherapy dose: range 500 to 2500 cGy *N* of participants hepatectomy: nm *N* of participants BMT: 4/27 (14.8%) *N* of participants blood transfusion: nm

French 2012 *(Continued)*

Outcomes	Method of detection of hepatic late adverse effects: ALT, AST, ALP, bilirubin (frequency of testing nm) Definition of hepatic late adverse effects: ALT > upper limit of normal (40 U/L); AST > upper limit of normal (36 U/L); ALP > upper limit of normal (140 U/L); unconjugated bilirubin > upper limit of normal (16 µmol/L); conjugated bilirubin > upper limit of normal (2 µmol/L) *N* of participants hepatic late adverse effects at end of follow-up: elevated liver enzymes: 3/23 (13.0%), ALT: 2/23 (8.7%), AST: 3/23 (13.0%), ALP: 1/23 (4.3%), unconjugated bilirubin: 2/23 (8.7%), conjugated bilirubin: 0/23 (0%) Risk factors: not evaluated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	High risk	Described study group consisted of less than 90% of the original cohort and was no random sample of the original cohort with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 60% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Well defined study group	High risk	Type of chemotherapy and number of participants with hepatitis virus infection were not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

Frisk 1998

Methods	Retrospective and prospective cohort study
Participants	*N* of participants original cohort: 40 *N* of participants described study group: 40 *N* of participants study group of interest: 40 *N* of participants with liver function tests: 40 Tumour: ALL, AML, NHL, HL (n = 30), non-malignant disease (n = 10) Time period diagnosis/treatment: from 1985 onwards Age at diagnosis: nm (age at BMT: median 7.6 (0.5 to 18.2) yr[a] Age at follow-up: nm F/M%: 39/61[a] BMI: nm *N* of participants hepatitis virus infection: 1/40 (2.5%) HCV-RNA^{+} (persistent HCV)

Frisk 1998 *(Continued)*

	N of participants acute liver disease: 52/64 (81.3%) elevated aminotransferases and/or bilirubin early after BMT[a]; 3/64 (4.7%) SOS[a]; 4/64 (6.3%) acute GVHD[a] Follow-up duration: median 5.0 (1.0 to 10.0) yr after BMT Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: minimal 33/40 (82.5%); chemotherapy type: prednisone, teniposide, daunorubicin, vincristine, cyclophosphamide, busulphan, BCNU, etoposide, cytarabine, cyclosporin and methotrexate; chemotherapy dose: nm *N* of participants radiotherapy involving the liver: 20/40 (50.0%); radiotherapy field: TBI; radiotherapy dose: 7.5 Gy *N* of participants hepatectomy: nm *N* of participants BMT: 40/40 (100%) *N* of participants blood transfusion: minimal 1/40 (2.5%)
Outcomes	Method of detection of hepatic late adverse effects: ALT, AST, ALP, bilirubin, PTT (measured annually 1 yr after BMT) Definition of hepatic late adverse effects: nm *N* of participants hepatic late adverse effects at end of follow-up: 6/40 (15.0%) Risk factors: not evaluated
Notes	[a] Data of 64 participants with BMT

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Low risk	Described study group consisted of more than 90% of the original cohort
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Well defined study group	Low risk	Type of chemotherapy, location of radiotherapy and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise

Green 2019

Methods	Cohort study
Participants	*N* of participants original cohort: 4421 *N* of participants described study group: 2753

Green 2019 *(Continued)*

	N of participants study group of interest: 2753
	N of participants with liver function tests: 2751
	Tumour: various
	Time period diagnosis/treatment: 1962-2000
	Age at diagnosis: median 7.4 (interquartile range 3.3 to 13.2) yr
	Age at follow-up: median 31.4 (interquartile range 25.8 to 37.8) yr
	F/M%: 49/51
	BMI: 763 (27.7%) overweight, 959 (34.9%) obese
	N of participants hepatitis virus infection: 7/73 (9.6%) hepatitis B seropositive, 98/1578 (6.2%) hepatitis C seropositive
	N of participants acute liver disease: 12 (0.4%) SOS
	Follow-up duration: median 23.2 (interquartile range 17.6 to 29.7) yr from diagnosis
	Completion of follow-up: 99.9%
Interventions	*N* of participants chemotherapy: nm
	Chemotherapy type: busulfan (n = 23), carmustine (n = 12), melphalan (n = 5), dactinomycin (n = 400), asparaginase (n = 918), methotrexate (n = 1328), high-dose methotrexate (n = 747), mercaptopurine (n = 1072), asparaginase (n = 17), thioguanine (n = 26)
	Chemotherapy dose: median 15,212.9 (interquartile range 4064.5 to 21,697.3) mg/m^2 high-dose methotrexate, doses of the other chemotherapeutics not mentioned
	N of participants radiotherapy involving the liver: 437 (15.9%)
	Radiotherapy field: hepatic irradiation (n = 368), TBI (n = 69)
	Radiotherapy dose: median percentage of liver that received 10 Gy was 51.4%, median percentage of liver that received 15 Gy was 34.6%, median percentage of liver that received 20 Gy was 25.3%
	N of participants hepatectomy: 24 (0.9%)
	N of participants BMT: 76 (2.8%), allogeneic HSCT 47 (1.7%), autologous HSCT 29 (1.1%) (2 participants included who underwent both allogeneic and autologous HSCT)
	N of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: single measurement of ALT
	Definition of hepatic late adverse effects: ALT > upper limit of normal (≥ 19 U/L for females, ≥ 30 U/L for males, ≥ 40 U/L according to institutional standards)
	N of participants hepatic late adverse effects at end of follow-up: ALT > upper limit of normal according to sex-specific values: 1137/2751 (41.3%); 1058/2751 (38.5%) grade 1, 56/2751 (2.0%) grade 2, 23/2751 (0.8%) grade 3, 0/2751 (0.0%) grade 4;
	ALT > upper limit of normal according to institutional values: 419/2751 (15.2%); 17/1225 (1.4%) deceased participants died due to liver disease
	Risk factors ALT > upper limit of normal according to sex-specific values using multivariable Poisson regression analysis:
	- Radiotherapy involving liver treated to ≥ 15 Gy per 10% volume increase (RR 1.06; 95% CI 1.03 to 1.08)
	- Busulfan (RR 1.54; 95% CI 1.02 to 2.33)

Green 2019 *(Continued)*

	- Thioguanine (RR 1.38; 95% CI 1.02 to 1.85) - Hepatic surgery (RR 1.90; 95% CI 1.45 to 2.49 - Older age at evaluation per yr (RR 1.01; 95% CI 1.00 to 1.01) - BMI ≥ 25 (RR 1.60; 95% CI 1.42 to 1.81) - Hepatitis C (RR 1.76; 95% CI 1.52 to 2.02) - Metabolic syndrome (RR 1.40; 95% CI 1.26 to 1.55) - Statins (atorvastatin, rosuvastatin, simvastatin) (RR 1.20; 95% CI 1.02 to 1.42) - Non-Hispanic white ethnicity (RR 1.37; 95% CI 1.18 to 1.58) (Analysis with radiotherapy involving liver treated to ≥ 20 Gy provided comparable results)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	High risk	Described study group consisted of less than 90% of the original cohort and was no random sample of the original cohort with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Adjustment important confounders	Low risk	Important prognostic factors and follow-up were taken into account
Well defined study group	Low risk	Type of chemotherapy and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise
Well defined risk estimation	Low risk	Relative risks were calculated

Guido 1991

Methods	Cohort study
Participants	*N* of participants original cohort: nm *N* of participants described study group: 54 with liver biopsy within 3 months after end chemotherapy *N* of participants study group of interest: 54 *N* of participants with liver function tests: 19 with abnormal liver function 3 months after chemotherapy Tumour: ALL

Guido 1991 *(Continued)*

	Time period diagnosis/treatment: 1979-1988 Age at diagnosis: mean 5.0, median 4.5 (1.5 to 11.0) yr[a] Age at follow-up: nm F/M%: 49/51[a] BMI: nm *N* of participants hepatitis virus infection: 6/19 (31.6%) anti-HCV$^+$, 4/19 (21.1%) HBsAntigen$^+$ of whom 1/19 (5.3%) anti-HDV$^+$ co-infection *N* of participants acute liver disease: 19/19 (100%) elevated ALT during chemotherapy; liver biopsy 3 months after end chemotherapy: 7/19 (36.8%) fibrosis, 8/19 (42.1%) acute hepatitis, 2/19 (10.5%) chronic persistent hepatitis, 1/19 (5.3%) chronic lobular hepatitis, 1/19 (5.3%) chronic active hepatitis and 0/19 (0.0%) cirrhosis Follow-up duration: mean 3.2 (2 to 7) yr after end of treatment[a] Completion of follow-up: 35.2%
Interventions	*N* of participants chemotherapy: 19/19 (100%); chemotherapy type: vincristine, prednisone, L-asparaginase, doxorubicin, daunorubicin, methotrexate, 6-mercaptopurine, cytosine arabinoside, 6-thioguanine, cyclophosphamide, hydroxyurea, BCNU; chemotherapy dose: nm *N* of participants radiotherapy involving the liver: nm; radiotherapy field: nm; radiotherapy dose: nm *N* of participants hepatectomy: nm *N* of participants BMT: nm *N* of participants blood transfusion: 19/19 (100%)
Outcomes	Method of detection of hepatic late adverse effects: ALT (measured 3-6 monthly 1 yr after the end of treatment) Definition of hepatic late adverse effects: elevated ALT *N* of participants hepatic late adverse effects at end of follow-up: 16/19 (84.2%) Risk factors: not evaluated
Notes	[a] Data of 72 participants with ALL with liver biopsy within 3 months after chemotherapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	High risk	Outcome was assessed for less than 60% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Well defined study group	Low risk	Type of chemotherapy and number of participants with hepatitis virus infection were mentioned

Guido 1991 *(Continued)*

Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise

Gunn 2016

Methods	Retrospective longitudinal cohort study
Participants	*N* of participants original cohort: nm *N* of participants described study group: 276 *N* of participants study group of interest: 276 *N* of participants with liver function tests: 267 Tumour: various Time period diagnosis/treatment: nm Age at diagnosis: mean 5.4 (range 0.0 to 17.3) yr[a] Age at follow-up: mean 18.0 (range 6.8 to 37.9) yr[a] F/M%: 48/52 BMI: 89 (32.2%) overweight[a] *N* of participants hepatitis virus infection: nm *N* of participants acute liver disease: nm Follow-up duration: ≥ 5 yr from end of treatment Completion of follow-up: 96.7%
Interventions	*N* of participants chemotherapy: 272 (98.6%)[a] Chemotherapy type: nm (intrathecal chemotherapy 131 (47.5%)[a] Chemotherapy dose: nm *N* of participants radiotherapy involving the liver: at least 13 (4.7%)[a] Radiotherapy field: TBI Radiotherapy dose: nm *N* of participants hepatectomy: nm *N* of participants BMT: 32 (11.6%)[a] *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT and AST Definition of hepatic late adverse effects: elevated ALT and/or AST not further specified *N* of participants hepatic late adverse effects at end of follow-up: 29/267 (10.9%) hypertransaminasaemia

Gunn 2016 *(Continued)*

	Risk factors: prevalence hypertransaminasaemia in participants treated with vs without cranial radiotherapy: 7.6% vs 7.3%, P = 0.003; prevalence hypertransaminasaemia in participants with vs without overweight: 17.6% vs 8.2% (P = 0.04) (univariable)
Notes	[a] Data of the described study group

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	High risk	Type of chemotherapy and number of participants with hepatitis virus infection were not mentioned
Well defined follow-up	High risk	Exact follow-up duration of the study group was not mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise
Well defined risk estimation	Low risk	Chi-square test and t-tests were performed

Hudson 2013

Methods	Cohort study
Participants	*N* of participants original cohort: 2843 *N* of participants described study group: 1713 *N* of participants study group of interest: 920[a] *N* of participants with liver function tests: 920 Tumour: various Time period diagnosis/treatment: 1962-2001 Age at diagnosis: mean 7.5 (± 5.5) yr; median 6.0 (0.0 to 24.0) yr[b] Age at follow-up: median 32 (18 to 60) yr[b] F/M%: 51/49[b] BMI: 624/1713 (36.4%) BMI > 30.0[b] *N* of participants hepatitis virus infection: 97/1713 (5.7%) anti-HCV$^+$ and 12/1713 (0.7%) HBsAg$^+$ and anti-HBc$^+$

Hudson 2013 *(Continued)*

	N of participants acute liver disease: nm Follow-up duration: mean 25.6 (± 7.6) yr from diagnosis[b]; median 25.1 (10.9 to 47.9) yr from diagnosis[b] Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: 834/920 (90.7%) at risk chemotherapy; chemotherapy type: mercaptopurine and thioguanine; chemotherapy dose: intravenous mercaptopurine: median 1118.6 (200.0 to 12,000.0) mg/m^2, oral mercaptopurine: median 21,405.0 (551.0 to 71,288.0) mg/m^2 *N* of participants radiotherapy involving the liver: 87/920 (9.5%) at risk radiotherapy involving liver; radiotherapy field: abdomen; radiotherapy dose: median 2383 (450 to 6840) cGy[b] *N* of participants hepatectomy: nm *N* of participants BMT: 23/1713 (1.3%) haematopoietic cell transplantation[b] *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT, AST, bilirubin (frequency of testing nm) Definition of hepatic late adverse effects: ALT > upper limit of normal (40 U/L), AST > upper limit of normal (40 U/L) or bilirubin > upper limit of normal (1 mg/dL) *N* of participants hepatic late adverse effects at end of follow-up: at risk: 119/920 (13.0%, 95% CI 10.8 to 15.3), mercaptopurine/thioguanine: 109/834 (13.1%, 95% CI 10.9 to 15.5), radiotherapy involving the liver: 10/87 (11.4%, 95% CI 5.7 to 20.1); not at risk: 86/793 (10.9%, 95% CI 8.8 to 13.2); grading according to Common Terminology Criteria for Adverse Events: 32 (15.6%) grade 1, 132 (64.4%) grade 2, 38 (18.5%) grade 3, 3 (1.5%) grade 4; Risk factors: high risk cancer treatment exposure (mercaptopurine, thioguanine, and/or radiotherapy involving the liver) explained 14.5% (95% CI -10.7 to 33.9) (P > 0.05) of the observed liver dysfunction (univariable)
Notes	[a] High-risk treatment exposure: CCS treated with mercaptopurine, thioguanine and/or radiotherapy involving the liver (dose ≥ 30 Gy) [b] Data of the described study group

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	High risk	Described study group consisted of less than 90% of the original cohort and was no random sample of the original cohort with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for mores than 90% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	Low risk	Type of chemotherapy, radiotherapy location, and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned

Hudson 2013 *(Continued)*

Well defined outcome	Low risk	Outcome definition was objective and precise
Well defined risk estimation	Low risk	Attributible fraction was calculated

Hyodo 2012

Methods	Retrospective cohort study
Participants	*N* of participants original cohort: nm *N* of participants described study group: 34 *N* of participants study group of interest: 34 *N* of participants with liver function tests: 34 Tumour: malignant disease (n = 21): ALL, AML, CML, NHL, non-malignant disease (n = 13): AA, other Time period diagnosis/treatment: 1982-1997 Age at diagnosis: median 10.0 (0.7 to 15.8) yr at SCT Age at follow-up: median 25.1 (18.0 to 27.7) yr F/M%: 0/100 BMI: median 19.3 (13.8 to 26.2) kg/m^2 *N* of participants hepatitis virus infection: 2/34 (5.9%) HCV-RNA^+ (persistent HCV) *N* of participants acute liver disease: nm Follow-up duration: median 16.3 (6.7 to 27.7) yr after SCT Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: 34/34 (100%); chemotherapy type: cyclophosphamide, methotrexate, cyclosporine; chemotherapy dose: nm *N* of participants radiotherapy involving the liver: 28/34 (82.4%); radiotherapy field: thoraco-abdominal (n = 8), TBI (n = 20); radiotherapy dose: 8-12 Gy TBI; 6-8 Gy TAI *N* of participants hepatectomy: nm *N* of participants BMT: 34/34 (100%) allogeneic stem cell transplantation *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT, AST, γGT (frequency of testing nm) Definition of hepatic late adverse effects: elevated ALT, AST, γGT *N* of participants hepatic late adverse effects at end of follow-up: 0/34 (0%) elevated liver enzymes (1 participant transient increase in transaminase levels) Risk factors: median γGT levels, albeit the normal range, were significantly higher in participants with fatty liver as compared to participants without fatty liver (P = 0.042); median ALT and AST levels were not significantly different between participants with and without fatty liver (P > 0.05) (univariable)

Hyodo 2012 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	Low risk	Type of chemotherapy, radiotherapy location, and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise
Well defined risk estimation	Low risk	Mean difference was calculated

Jagt 2009

Methods	Retrospective cohort study
Participants	*N* of participants original cohort: nm *N* of participants described study group: 91 *N* of participants study group of interest: 91 *N* of participants with liver function tests: 64 Tumour: Wilms' tumour Time period diagnosis/treatment: 1986-2006 Age at diagnosis: range 0.2 to 10.9 yr[a] Age at follow-up: nm F/M%: 40/60[a] BMI: nm *N* of participants hepatitis virus infection: nm *N* of participants acute liver disease: minimal 13/64 (20.3%) SOS Follow-up duration: ≥ 5 yr after end of treatment

Jagt 2009 *(Continued)*

	Completion of follow-up: 70.3%
Interventions	*N* of participants chemotherapy: 64/64 (100%); chemotherapy type: vincristine, actinomycin, epirubicin and doxorubicin; chemotherapy dose: weekly 1.5 mg/kg vincristine, 4 courses 15 µg/kg actinomycin on 3 subsequent days, or 2 courses 15 µg/kg actinomycin on 3 subsequent days, or 2 courses 45 µg/kg actinomycin once every 2 weeks, and 2 courses 50 mg/m^2 epirubicin or doxorubicin *N* of participants radiotherapy involving the liver: nm; radiotherapy field: nm; radiotherapy dose: nm *N* of participants hepatectomy: nm *N* of participants BMT: nm *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT, AST, γGT, ALP (frequency of testing nm) Definition of hepatic late adverse effects: any value higher than age-dependent upper limit of normal *N* of participants hepatic late adverse effects at end of follow-up: 33/64 (51.6%) Risk factors: not evaluated
Notes	[a] Data of 91 participants in the described study group

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 60% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Well defined study group	High risk	Number of participants with hepatitis virus infection was not mentioned
Well defined follow-up	High risk	Length of follow-up was not mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

Landier 2012

Methods	Cohort study
Participants	*N* of participants original cohort: nm *N* of participants described study group: 370 *N* of participants study group of interest: 266[a] *N* of participants with liver function tests: 263 Tumour: various Time period diagnosis/treatment: nm

Landier 2012 *(Continued)*

	Age at diagnosis: median 10.2 (0.3 to 21.9) yr Age at follow-up: median 28.3 (8 to 58) yr F/M%: 45/55 BMI: nm *N* of participants hepatitis virus infection: 13/146 (8.9%) of tested participants HCV-RNA$^+$ (persistent HCV) (9 diagnosed before routine screening, 4 during screening) and 0/29 (0%) tested participants HB-sAg$^+$and anti-HBc$^+$ *N* of participants acute liver disease: 44.2% out of 93 CCS treated with HSCT have chronic graft-versus-host-disease Follow-up duration: median 10.4 (5.0 to 37.8) yr from diagnosis Completion of follow-up: 98.9%
Interventions	*N* of participants chemotherapy: 351/370 (94.9%)[b]; chemotherapy type: methotrexate, mercaptopurine, thioguanine, cytarabine; chemotherapy dose: high-dose methotrexate: median 7970 (1000 to 257,000) mg/m^2, low-dose methotrexate: median 1295 (20 to 13,400) mg/m^2, mercaptopurine: median 40,300 (250 to 92,400) mg/m^2, thioguanine: median 1580 (520 to 48,730) mg/m^2, high-dose cytarabine: median 11400 (1750 to 53,130) mg/m^2, low-dose cytarabine: median 1200 (75 to 18,000) mg/m^2 *N* of participants radiotherapy involving the liver: nm; radiotherapy field: abdomen; radiotherapy dose: median 38 (30 to 76) Gy[b] *N* of participants hepatectomy: nm *N* of participants BMT: 93/263 (35.4%) haematopoietic cell transplantation (44% autologous, 56% allogeneic) *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT, AST, bilirubin (frequency of testing nm) Definition of hepatic late adverse effects: ALT ≥ 2 times upper limit of normal (> 56 U/L) or AST ≥ 2 times upper limit of normal (> 46 U/L) or total bilirubin > upper limit of normal (1.5 mg/dL) *N* of participants hepatic late adverse effects at end of follow-up: 10/263 (3.8%) diagnosed during follow-up; 3 diagnosed before routine screening, so total prevalence: 13/266 (4.9%); ALT: 6/263 (2.3%), AST: 6/263 (2.3%), ALT and AST: 5/263 (1.9%), ALT or AST: 7/263 (2.7%), bilirubin: 3/263 (1.1%) Risk factors: not evaluated
Notes	[a] High-risk treatment exposure: CCS treated with methotrexate, mercaptopurine, thioguanine, cytarabine, radiotherapy involving the liver (dose ≥ 30 Gy) and/or haematopoietic cell transplantation [b] Data of the described study group

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest

Landier 2012 *(Continued)*

Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Well defined study group	Low risk	Type of chemotherapy, radiotherapy location, and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

Locasciulli 1983

Methods	Retrospective and prospective cohort study
Participants	*N* of participants original cohort: nm *N* of participants described study group: 70 with abnormal liver function during chemotherapy *N* of participants study group of interest: 70 *N* of participants with liver function tests: 56 Tumour: ALL, ANLL Time period diagnosis/treatment: 1972-1981 Age at diagnosis: mean 8 (4 to 19) yr[a] Age at follow-up: nm F/M%: 43/57[b] BMI: nm *N* of participants hepatitis virus infection: 30/56 (53.6%) HBV markers (i.e. antigens or antibodies for HBV) *N* of participants acute liver disease: 56/56 (100%) elevated ALT/AST during chemotherapy; liver biopsy in 38 participants at end chemotherapy: 5/38 (13.1%) chronic lobular hepatitis, 17/38 (44.7%) chronic persistent hepatitis and 9/38 (23.6%) chronic active hepatitis Follow-up duration: mean 2.0 (0.5 to 7.0) yr after end of treatment Completion of follow-up: 80.0%
Interventions	*N* of participants chemotherapy: 56/56 (100%); chemotherapy type: vincristine, prednisone, 6-mercaptopurine, methotrexate, vinblastine, L-asparaginase, daunorubicin, cytosine arabinoside, doxorubicin, cyclophosphamide, 6-thioguanine; chemotherapy dose: nm *N* of participants radiotherapy involving the liver: nm; radiotherapy field: nm; radiotherapy dose: nm *N* of participants hepatectomy: nm *N* of participants BMT: nm *N* of participants blood transfusion: 53/56 (94.6%)
Outcomes	Method of detection of hepatic late adverse effects: ALT, AST (measured 3-6 monthly) Definition of hepatic late adverse effects: ALT/AST > 3 times upper limit of normal (60 IU/L) for ≥ 6 months

Locasciulli 1983 *(Continued)*

	N of participants hepatic late adverse effects at end of follow-up: ≥ 6 months: 22/56 (39.3%), < 6 months: 10/56 (17.9%) Risk factors: cleared or persistent chronic HBV infection: 17/22 (77.3%) with persistently high transaminases HBV markers versus 3/24 (12.5%) with normal transaminases HBV markers (P < 0.001); histological diagnosis of chronic hepatitis: 19/27 (70.4%) with histological diagnosis of chronic hepatitis persistently elevated transaminases versus 1/4 (25.0%) with minimal changes persistently elevated transaminases (P < 0.005) (univariable)
Notes	[a] Data of 103 participants with ALL/ANLL [b] Data of 70 participants in the original cohort

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 60% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	Low risk	Type of chemotherapy and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise
Well defined risk estimation	Low risk	Chi^2 was calculated

Locasciulli 1985

Methods	Prospective cohort study
Participants	*N* of participants original cohort: nm *N* of participants described study group: 89 with abnormal liver function during chemotherapy *N* of participants study group of interest: 89 *N* of participants with liver function tests: 48 Tumour: ALL, ANLL Time period diagnosis/treatment: 1979 Age at diagnosis: mean 4.8 (0.3 to 14.0) yr[a] Age at follow-up: nm

Locasciulli 1985 *(Continued)*

	F/M%: 46/54[a]
	BMI: nm
	N of participants hepatitis virus infection: 23/48 (47.9%) HBsAntigen$^+$
	N of participants acute liver disease: 48/48 (100%) elevated ALT during chemotherapy
	Follow-up duration: mean 2.8 (0.5 to 4.1) yr after end of treatment
	Completion of follow-up: 53.9%
Interventions	*N* of participants chemotherapy: 48/48 (100%); chemotherapy type: vincristine, prednisone, 6-mercaptopurine, methotrexate, L-asparaginase, cytosine arabinoside, 6-thioguanine, doxorubicin, cyclophosphamide, BCNU, daunorubicin; chemotherapy dose: nm
	N of participants radiotherapy involving the liver: nm; radiotherapy field: nm; radiotherapy dose: nm
	N of participants hepatectomy: nm
	N of participants BMT: nm
	N of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT (frequency of testing nm)
	Definition of hepatic late adverse effects: ALT > 3 times upper limit of normal (60 IU/L) for ≥ 6 months
	N of participants hepatic late adverse effects at end of follow-up: 33/48 (68.8%)
	Risk factors: not evaluated
Notes	[a] Data of 164 participants with ALL/ANLL

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	High risk	Outcome was assessed for less than 60% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Well defined study group	Low risk	Type of chemotherapy and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

Locasciulli 1991a

Methods	Cohort study
Participants	*N* of participants original cohort: 174

Locasciulli 1991a *(Continued)*

	N of participants described study group: 50 with abnormal liver function during chemotherapy
	N of participants study group of interest: 50
	N of participants with liver function tests: 50
	Tumour: ALL (n = 40), AML (n = 8), CML (n = 1), RAEB (n = 1)
	Time period diagnosis/treatment: 1969-1989
	Age at diagnosis: mean 5.8 (0.8 to 16.6) yr
	Age at follow-up: nm
	F/M%: 40/60
	BMI: nm
	N of participants hepatitis virus infection: 12/50 (24.0%) anti-HCV$^+$ and RIBA$^+$, and 14/50 (28.0%) HB-sAntigen$^+$
	N of participants acute liver disease: 50/50 (100%) elevated ALT during chemotherapy; liver biopsy in 37 participants at end chemotherapy: 7/37 (18.9%) nonspecific reactive hepatitis, 13/37 (35.1%) chronic lobular hepatitis, 12/37 (32.4%) chronic persistent hepatitis and 10/37 (27.0%) chronic active hepatitis
	Follow-up duration: mean 6.2 ± 3.4 (1.0 to 12.6) yr after end of treatment
	Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: 50/50 (100%); chemotherapy type: nm; chemotherapy dose: nm
	N of participants radiotherapy involving the liver: nm; radiotherapy field: nm; radiotherapy dose: nm
	N of participants hepatectomy: nm
	N of participants BMT: 13/50 (26.0%)
	N of participants blood transfusion: 48/50 (96.0%)
Outcomes	Method of detection of hepatic late adverse effects: ALT (measured 3-6 monthly)
	Definition of hepatic late adverse effects: ALT > upper limit of normal (40 IU/L)
	N of participants hepatic late adverse effects at end of follow-up: 20/50 (40.0%)
	Risk factors: Chronic HCV infection: 11/12 (91.7%) with chronic HCV infection persistently elevated ALT versus 8/27 (29.6%) without chronic HCV infection persistently elevated ALT (P = 0.0012) (univariable)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	High risk	Described study group consisted of less than 90% of the original cohort and was no random sample of the original cohort with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding

Locasciulli 1991a *(Continued)*

Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	High risk	Type of chemotherapy was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise
Well defined risk estimation	Low risk	Mean difference was calculated

Locasciulli 1997a

Methods	Prospective cohort study
Participants	*N* of participants original cohort: 125 *N* of participants described study group: 114 *N* of participants study group of interest: 114 *N* of participants with liver function tests: 114 Tumour: ALL, AML Time period diagnosis/treatment: 1968-1982 Age at diagnosis: mean 4 ± 2.6 yr Age at follow-up: nm F/M%: 48/52 BMI: nm *N* of participants hepatitis virus infection: 28/114 (24.6%) HCV-RNA^{+} (persistent HCV), and 19/114 (16.7%) anti-HCV^{+}and HCV-RNA^{-} *N* of participants acute liver disease: 54/111 (48.7%) elevated ALT at end chemotherapy; liver biopsy in 36 participants at end chemotherapy: 5/36 (13.9%) nonspecific reactive hepatitis, 9/36 (25.0%) chronic lobular hepatitis, 15/36 (41.7%) chronic persistent hepatitis and 7/36 (19.4%) chronic active hepatitis Follow-up duration: mean 17 ± 3.2 (13 to 27) yr after end of treatment Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: 114/114 (100%); chemotherapy type: nm; chemotherapy dose: nm *N* of participants radiotherapy involving the liver: nm; radiotherapy field: nm; radiotherapy dose: nm *N* of participants hepatectomy: nm *N* of participants BMT: nm *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT (measured yearly), liver biopsy (n = 2 at follow-up of 5 and 7 yr, respectively)

Locasciulli 1997a *(Continued)*

	Definition of hepatic late adverse effects: ALT > upper limit of normal (42 IU/L) *N* of participants hepatic late adverse effects at end of follow-up: ALT: 33/114 (28.9%) of whom 4/114 (3.5%) had constantly abnormal values and 29/114 (25.4%) fluctuations from normal to abnormal values; liver biopsy: 1/2 (50.0%) chronic persistent hepatitis, 1/2 (50.0%) chronic lobular hepatitis Risk factors: chronic HCV infection: 22/28 (78.6%) with chronic HCV infection elevated ALT versus 11/86 (12.8%) without chronic HCV infection elevated ALT (P = 0.008) (univariable)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Low risk	Described study group consisted of more than 90% of the original cohort
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding; unclear if the outcome assessors of the biopsies were blinded
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	High risk	Type of chemotherapy was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise
Well defined risk estimation	Low risk	Chi^2 was calculated

Locasciulli 1997b

Methods	Prospective cohort study
Participants	*N* of participants original cohort: 53 *N* of participants described study group: 53 *N* of participants study group of interest: 53 *N* of participants with liver function tests: 53 Tumour: malignant disease (n = 42): ALL, AML, CML, JCML, Histiocytosis X, non-malignant disease (n = 11): SAA, RAEB Time period diagnosis/treatment: 1985-1995 Age at diagnosis: nm (age at BMT: mean 9.4 (0.9 to 18.0) yr[a] Age at follow-up: nm F/M%: 34/66[a]

Locasciulli 1997b *(Continued)*

	BMI: nm *N* of participants hepatitis virus infection: minimal 9/53 (17.0%) HCV-RNA^{+} (persistent HCV), minimal 5/53 (9.4%) anti-HCV^{+} and HCV-RNA^{-}, and 2/53 (3.8%) HBsAntigen^{+} *N* of participants acute liver disease: 82/111 (73.9%) elevated ALT after BMT[a]; 4/111 (3.6%) SOS leading to multi-organ failure[a] Follow-up duration: range 1.3 to 10.9 yr after BMT Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: 53/53 (100%); chemotherapy type: cyclophosphamide, cytarabine, vincristine, etoposide, busulphan, melphalan, cyclosporine and methotrexate; chemotherapy dose: 120 mg/kg cyclophosphamide was given as 2 daily doses of 60 mg/kg, alone, or in combination with high-dose cytarabine 3 mg/m^2 for 2 days, high-dose vincristine 4 mg/m^2 in 4 days, etoposide 60mg/kg in 1 day, busulphan 16 mg/kg as 4 daily doses and melphalan 140 mg/m^2. Children with SAA were conditioned with 200 mg/kg cyclophosphamide given in divided doses on 4 days. Cyclosporine and methotrexate dose: nm *N* of participants radiotherapy involving the liver: nm (76/111 (68.5%))[a]; radiotherapy field: TBI; radiotherapy dose: 12 Gy *N* of participants hepatectomy: nm *N* of participants BMT: 53/53 (100%) *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT (measured 3-monthly) Definition of hepatic late adverse effects: ALT > upper limit of normal (42 IU/L) for ≥ 6 months *N* of participants hepatic late adverse effects at end of follow-up: 28/53 (52.8%) Risk factors: not evaluated
Notes	[a] Data of 111 participants with BMT

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Low risk	Described study group consisted of more than 90% of the original cohort
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Well defined study group	Low risk	Type of chemotherapy, location of radiotherapy, and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

Matsuzaki 2001

Methods	Prospective cohort study
Participants	*N* of participants original cohort: nm *N* of participants described study group: 132 *N* of participants study group of interest: 132 *N* of participants with liver function tests: 105 Tumour: ALL Time period diagnosis/treatment: 1984-1990 Age at diagnosis: nm Age at follow-up: nm F/M%: 42/58[a] BMI: nm (one participant with obesity) *N* of participants hepatitis virus infection: 9/105 (8.6%) HCV infection (not further specified in paper) *N* of participants acute liver disease: nm Follow-up duration: nm Completion of follow-up: 79.5%
Interventions	*N* of participants chemotherapy: 105/105 (100%); chemotherapy type: vincristine, prednisolone, L-asparaginase, daunorubicin, cytosine arabinoside, methotrexate, 6-mercaptopurine, enocitabine, doxorubicin, dexamethasone and cyclophosphamide[a]; chemotherapy dose: induction consisted of 4 times 2 mg/m^2 vincristine, 4 weeks 60 mg/m^2 prednisolone, 7 times 10,000 U/m^2 L-asparaginase, 2 times 25 mg/m^2 daunorubicin and 4 times 500 mg/m^2 cytosine arabinoside. Consolidation consisted of 300 + 400 mg/m^2 or 2 times 500 mg/m^2 methotrexate, 14 days 120 mg/m^2 6-mercaptopurine and 8 times 150 mg/m^2 enocitabine. Reinduction consisted of 4 times 2 mg/m^2 vincristine, 2 to 4 weeks 8 mg/m^2 dexamethasone, 4 times 1 g/m^2 high-dose cytosine arabinoside and 1 time 10,000 U/m^2 L-asparaginase. Maintenance consisted of 4 days 120 mg/m^2 6-mercaptopurine, 600 mg/m^2 intravenous cyclophosphamide, 4 days 70 mg/m^2 cyclophosphamide by mouth, 45 mg/m^2 daunorubicin, 200 mg/m^2 cytosine arabinoside, 4 days 10 mg/m^2 methotrexate and 2 mg/m^2 vincristine[a] *N* of participants radiotherapy involving the liver: 0 (0.0%); radiotherapy field: not applicable; radiotherapy dose: not applicable *N* of participants hepatectomy: nm *N* of participants BMT: 0 (0.0%) *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: transaminase (frequency of testing nm) Definition of hepatic late adverse effects: transaminase < 100 IU/L *N* of participants hepatic late adverse effects at end of follow-up: 19/105 (18.1%) Risk factors: not evaluated
Notes	[a] Data of 187 participants with ALL

Matsuzaki 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 60% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Well defined study group	Low risk	Type of chemotherapy and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	High risk	Length of follow-up was not mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise

Mulder 2013

Methods	Cohort study
Participants	*N* of participants original cohort: 1795 *N* of participants described study group: 1404 *N* of participants study group of interest: 1404 *N* of participants with liver function tests: 1362 Tumour: various Time period diagnosis/treatment: 1966-2003 Age at diagnosis: median 5.9 (0.0 to 17.8) yr Age at follow-up: median 19.5 (5.8 to 47) yr F/M%: 46/54 BMI: nm *N* of participants hepatitis virus infection: 0/1362 (0.0%) (participants with hepatitis virus infection excluded according to eligibility criteria for the study) *N* of participants acute liver disease: 0/1362 (0.0%) SOS (participants with SOS excluded according to eligibility criteria for the study) Follow-up duration: median 12.4 (5.0 to 36.1) yr from diagnosis Completion of follow-up: 97.0%
Interventions	*N* of participants chemotherapy: 1204/1362 (88.4%); chemotherapy type: methotrexate (n = 392), mercaptopurine (n = 352), thioguanine (n = 98), dactinomycin (n = 397), busuphan (n = 10), other antimetabolites (n = 426), other cytotoxic antibiotics (n = 633), other alkylating agents (n = 715), plant alkaloids (n = 1115), other chemotherapeutics (n = 837); chemotherapy dose: nm

Mulder 2013 *(Continued)*

	N of participants radiotherapy involving the liver: 123/1362 (9.0%); radiotherapy field: abdomen (n = 102), TBI (n = 21); radiotherapy dose: median 20.0 (5.0 to 46.0) yr *N* of participants hepatectomy: 35/1362 (2.6%) *N* of participants BMT: 61/1362 (4.5%) *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: single measurement ALT and γGT Definition of hepatic late adverse effects: hepatocellular injury: ALT > upper limit of normal (≥ 34 U/L for females, ≥ 45 U/L for males and children < 15 years); biliary tract injury: γGT > upper limit of normal (≥ 40 U/L for females, ≥ 60 U/L for males, ≥ 56 U/L for children < 15 years) *N* of participants hepatic late adverse effects at end of follow-up: ALT or γGT > upper limit of normal: 118/1362 (8.7%); hepatocellular injury: 79/1362 (5.8%) ALT > upper limit of normal, 12/1362 (0.9%) ALT > two times upper limit of normal; biliary tract injury (1295 survivors tested): 68/1295 (5.3%) γGT > upper limit of normal, 12/1295 (0.9%) γGT > two times upper limit of normal; no participant had end-stage liver failure Risk factors: Risk factors ALT > upper limit of normal using multivariable logistic regression analysis: - Radiotherapy involving liver (OR 2.34; 95% CI 1.07 to 5.13) - Higher BMI z-score (OR 1.67; 95% CI 1.37 to 2.03) - Alcohol intake of > 14 units per week (OR 2.53; 95% CI 1.04 to 6.18) - Longer follow-up time (OR 1.10; 95% CI 1.05 to 1.15) - Non-significant factors (P > 0.05): methotrexate, mercaptopurine, thioguanine, dactinomycin, busulphan, other antimetabolites, other cytotoxic antibiotics, other alkylating agents, plant alkaloids, other chemotherapeutic agents, liver resection, gender, alcohol intake < 7 units per week, alcohol intake 7-14 units per week, age at cancer diagnosis; Risk factors γGT > upper limit of normal using multivariable logistic regression analysis: - Radiotherapy involving liver (OR 5.45; 95% CI 2.51 to 11.82) - Higher BMI z-score (OR 1.43; 95% CI 1.14 to 1.81) - Alcohol intake of > 14 units per week (OR 3.04; 95% CI 1.16 to 7.96) - Older age at cancer diagnosis (OR 1.08; 95% CI 1.01 to 1.15) - Longer follow-up time (OR 1.13; 95% CI 1.07 to 1.18) - Non-significant factors (P > 0.05): methotrexate, mercaptopurine, thioguanine, dactinomycin, busulphan, other antimetabolites, other cytotoxic antibiotics, other alkylating agents, plant alkaloids, other chemotherapeutic agents, liver resection, gender, alcohol intake < 7 units per week, alcohol intake 7-14 units per week
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	High risk	Described study group consisted of less than 90% of the original cohort and was no random sample of the original cohort with respect to cancer treatment

Mulder 2013 *(Continued)*

Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Adjustment important confounders	Low risk	Important prognostic factors and follow-up were taken into account
Well defined study group	Low risk	Type of chemotherapy and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise
Well defined risk estimation	Low risk	Odds ratios were calculated

Ratner 1986

Methods	Retrospective cohort study
Participants	*N* of participants original cohort: nm *N* of participants described study group: 39 *N* of participants study group of interest: 39 *N* of participants with liver function tests: 39 Tumour: ALL Time period diagnosis/treatment: 1971-1980 Age at diagnosis: nm Age at follow-up: nm F/M%: nm BMI: nm *N* of participants hepatitis virus infection: 5/39 (12.8%) HBsAntigen^{+} of whom 3/39 (7.7%) anti-HDV^{+} co-infection *N* of participants acute liver disease: 50/79 (63.3%) elevated ALT during maintenance therapy[a] Follow-up duration: range 1.0 to 8.3 yr after end of treatment Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: 39/39 (100%); chemotherapy type: vincristine, 6-mercaptopurine, methotrexate, asparaginase, cyclophosphamide, daunorubicin, hydroxyurea and prednisone; chemotherapy dose: nm *N* of participants radiotherapy involving the liver: nm; radiotherapy field: nm; radiotherapy dose: nm *N* of participants hepatectomy: nm

Ratner 1986 *(Continued)*

	N of participants BMT: nm
	N of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT (measured 6-monthly), liver biopsy (n = 3)
	Definition of hepatic late adverse effects: ALT > 2 times upper limit of normal (90 U/L)
	N of participants hepatic late adverse effects at end of follow-up: ALT: 9/39 (23.1%); liver biopsy: 3/3 (100%) cirrhosis
	Risk factors: not evaluated
Notes	[a] Data of 79 participants with ALL

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding; unclear if the outcome assessors of the biopsies were blinded
Well defined study group	Low risk	Type of chemotherapy and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

Rossetti 1991

Methods	Cohort study
Participants	*N* of participants original cohort: nm
	N of participants described study group: 145
	N of participants study group of interest: 145
	N of participants with liver function tests: 96
	Tumour: ALL
	Time period diagnosis/treatment: 1967-1983
	Age at diagnosis: nm
	Age at follow-up: range 6 to 26 yr
	F/M%: 49/51
	BMI: nm

Rossetti 1991 *(Continued)*

	N of participants hepatitis virus infection: 60/96 (62.5%) HBsAntigen$^+$ of whom 30/96 (31.3%) anti-HDV$^+$ co-infection *N* of participants acute liver disease: 40/96 (41.7%) elevated ALT during chemotherapy; liver biopsy in 72 participants within 3 months after chemotherapy: 27/72 (37.5%) chronic active hepatitis or cirrhosis and 10/72 (13.9%) chronic persistent/lobular hepatitis Follow-up duration: range 4 to 20 yr from diagnosis, ≥ 2.0 yr after end of treatment Completion of follow-up: 66.2%
Interventions	*N* of participants chemotherapy: 96/96 (100%); chemotherapy type: vincristine, L-asparaginase, doxorubicin, daunorubicin, methotrexate (high-dose) 6-mercaptopurine, cytosine arabinoside, 6-thioguanine, cyclophosphamide, hydroxyurea and BCNU; chemotherapy dose: nm *N* of participants radiotherapy involving the liver: nm; radiotherapy field: nm; radiotherapy dose: nm *N* of participants hepatectomy: nm *N* of participants BMT: nm *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT (measured 3-monthly), albumin (frequency of testing nm) Definition of hepatic late adverse effects: ALT > 2 times upper limit of normal (100 IU/L); Albumin nm *N* of participants hepatic late adverse effects at end of follow-up: ALT: 43/96 (44.8%); Albumin: 0/96 (0.0%) Risk factors: chronic HBV-HDV co-infection and chronic HBV infection: 27/30 (90.0%) with chronic HBV-HDV co-infection elevated ALT versus 10/26 (38.5%) with chronic HBV infection elevated ALT versus 6/40 (15.0%) without chronic HBV infection elevated ALT (P < 0.02) (univariable)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 60% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	Low risk	Type of chemotherapy and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

Rossetti 1991 *(Continued)*

Well defined risk estimation	Low risk	Chi^2 was calculated

Schempp 2016

Methods	Cohort study
Participants	*N* of participants original cohort: nm *N* of participants described study group: 63 *N* of participants study group of interest: 63 *N* of participants with liver function tests: nm Tumour: ALL (n = 21), AML (n = 13), brain/CNS tumour (n = 4), osteosarcoma (n = 2), Ewing sarcoma (n = 3), soft tissue sarcoma (n = 3), Hodgkin lymphoma (n = 3), non-Hodgkin lymphoma (n = 4), neuroblastoma (n = 2), Wilms tumour (n = 4), aplastic anaemia (n = 1), paroxysmal nocturnal haemoglobinuria (n = 1), histiocytosis (n = 1), leukodystrophy (n = 1) Time period diagnosis/treatment: nm Age at diagnosis: oncology participants treated without HSCT median 3.7 (range 0.9 to 17.9) yr, allogeneic HSCT participants median 3.8 (range 0.2 to 15.7) yr, autologous HSCT participants median 6.2 (range 2.2 to 18.9) yr Age at follow-up: oncology participants treated without HSCT median 18.8 (range 7.9 to 39.2) yr, allogeneic HSCT participants median 16.4 (range 6.2 to 34.6) yr, autologous HSCT participants median 20.8 (range 9.9 to 28) yr F/M%: 43/57 BMI: nm *N* of participants hepatitis virus infection: nm *N* of participants acute liver disease: nm Follow-up duration from diagnosis: oncology participants treated without HSCT median 10.4 (range 4.7 to 36.0) yr, allogeneic HSCT participants median 8.0 (range 4.4 to 25.0) yr, autologous HSCT participants median 9.1 (range 4.3 to 19.4) yr Completion of follow-up: unclear
Interventions	*N* of participants chemotherapy: nm Chemotherapy type: nm Chemotherapy dose: nm *N* of participants radiotherapy involving the liver: nm Radiotherapy field: nm Radiotherapy dose: nm *N* of participants hepatectomy: nm *N* of participants BMT: 36 (57.1%), 27 allogeneic HSCT, 9 autologous HSCT *N* of participants blood transfusion: 63 (100%)

Schempp 2016 *(Continued)*

Outcomes	Method of detection of hepatic late adverse effects: ALT, AST, bilirubin, iron overload Definition of hepatic late adverse effects: abnormal levels of ALT, AST and bilirubin not further specified; iron overload defined as serum ferritin > 1000 ng/mL *N* of participants hepatic late adverse effects at end of follow-up: total group 9/63 (14.3%), oncology participants treated without HSCT 3/27 (11.1%) of which 1 elevated AST and 1 elevated bilirubin, allogeneic HSCT participants 6/27 (22.2%) of which 5 elevated ALT and/or AST and 1 elevated bilirubin, autologous HSCT participants 0/9 (0%) Risk factors: serum ferritin not associated with liver abnormalities defined as elevated ALT, AST or bilirubin (univariable)
Notes	Although cancer treatment of the non-HSCT participants was not reported in this study, we assumed that those participants had been treated for their malignancy. The prevalence of hepatic late effects was presented as the best case scenario as it was unclear how many participants had a liver function test.

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Unclear risk	Unclear if the outcome was assessed for more than 60% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	High risk	Type of chemotherapy and number of participants with hepatitis virus infection were not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	High risk	The upper limits of normal for liver function measures were not described
Well defined risk estimation	High risk	No risk estimation reported

Seth 2017

Methods	Cohort study
Participants	*N* of participants original cohort: nm *N* of participants described study group: 300 *N* of participants study group of interest: 300 *N* of participants with liver function tests: nm

Seth 2017 *(Continued)*

	Tumour: ALL, AML, Ewing sarcoma, Hodgkin lymphoma, non-Hodgkin lymphoma, retinoblastoma, rhabdomyosarcoma, Langerhas cell histiocytosis, other Time period diagnosis/treatment: nm Age at diagnosis: median 5 (interquartile range 3.7 to 9.2) yr Age at follow-up: median 14 (interquartile range 12.1 to 14.4) yr F/M%: 4.6:1 BMI: nm *N* of participants hepatitis virus infection: 33/110 tested participants (30.0%) $HBsAg^+$ *N* of participants acute liver disease: nm Follow-up duration since diagnosis: median 9 (interquartile range 7.0 to 9.3) yr, longest 29 yr (all participants completed five years of follow up in the after-treatment completion clinic) Completion of follow-up: unclear
Interventions	*N* of participants chemotherapy: 300 (100%) Chemotherapy type: nm Chemotherapy dose: nm *N* of participants radiotherapy involving the liver: nm (maximum 2 participants, because 72 participants treated with radiotherapy. These included 60 ALL who received cranial RT, four Hodgkin lymphoma (neck and mediastinum), six retinoblastoma, one Ewing sarcoma, and one rhabdomyosarcoma). Radiotherapy field: nm Radiotherapy dose: nm *N* of participants hepatectomy: nm *N* of participants BMT: nm *N* of participants blood transfusion: 110 (36.7%)
Outcomes	Method of detection of hepatic late adverse effects: liver enzymes not further specified Definition of hepatic late adverse effects: nm *N* of participants hepatic late adverse effects at end of follow-up: 6/300 (2.0%) elevated liver enzymes and 1 participant died of liver failure Risk factors: not evaluated
Notes	The prevalence of hepatic late effects was presented as the best case scenario as it was unclear how many participants had a liver function test.

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment

Seth 2017 *(Continued)*

Complete follow-up assessment	Unclear risk	Unclear if the outcome was assessed for more than 60% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Well defined study group	High risk	Type of chemotherapy not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	High risk	The upper limits of normal for liver function measures were not described

Skou 2014

Methods	Cohort study
Participants	*N* of participants original cohort: 138 *N* of participants described study group: 105 *N* of participants study group of interest: 105 *N* of participants with liver function tests: 104 Tumour: AML Time period diagnosis/treatment: 1984-2003 Age at diagnosis: range 0 to 17 yr Age at follow-up: median 16 (5 to 37) yr F/M%: 56/44 BMI: nm *N* of participants hepatitis virus infection: 1/102 (1.0%) chronic active HBV (not further specified in paper); 2/102 (2.0%) chronic active HCV (not further specified in paper) *N* of participants acute liver disease: nm Follow-up duration: median 11 (4 to 25) yr from diagnosis Completion of follow-up: 99.0%
Interventions	*N* of participants chemotherapy: 104/104 (100%); chemotherapy type: cytarabine, anthracyclines, 6-thioguanine and etoposide; chemotherapy dose: 50-60 g/m^2 cytarabine, 300-450 mg/m^2 anthracyclines, 800-2400 mg/m^2 6-thioguanine and 1600 mg/m^2 etoposide *N* of participants radiotherapy involving the liver: 0/104 (0%); radiotherapy field: na; radiotherapy dose: na *N* of participants hepatectomy: 0/104 (0%) *N* of participants BMT: 0/104 (0%) *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT, AST, ALP, bilirubin, prothrombin ratio, albumin (frequency of testing nm)

Skou 2014 *(Continued)*

	Definition of hepatic late adverse effects: ALT > upper limit of normal, AST > upper limit of normal, ALP > upper limit of normal, bilirubin > upper limit of normal, prothrombin ratio nm, albumin nm *N* of participants hepatic late adverse effects at end of follow-up: ALT: 6/104 (5.8%); AST: 1/88 (1.1%); ALP: 11/99 (11.1%); bilirubin: 1/104 (1.0%); prothrombin ratio: 4/29 (13.8%); albumin: 14/97 (14.4%) Risk factors: not evaluated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	High risk	Described study group consisted of less than 90% of the original cohort and was no random sample of the original cohort with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Well defined study group	Low risk	Type of chemotherapy and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

Stringer 1995

Methods	Retrospective cohort study
Participants	*N* of participants original cohort: 26 *N* of participants described study group: 26 *N* of participants study group of interest: 26 *N* of participants with liver function tests: 26 Tumour: hepatoblastoma Time period diagnosis/treatment: 1981-1993 Age at diagnosis: median 1.3 (0.0 to 12.0) yr[a] Age at follow-up: nm F/M%: 39/61[a] BMI: nm *N* of participants hepatitis virus infection: nm *N* of participants acute liver disease: nm Follow-up duration: median 5.3 (0.1 to 12.2) yr

Stringer 1995 *(Continued)*

	Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: 24/26 (92.3%); chemotherapy type: cisplatin, doxorubicin, carboplatin and etoposide; chemotherapy dose: 3-weekly cisplatin (80-100 mg/m^2) and doxorubicin (50-60 mg/m^2) *N* of participants radiotherapy involving the liver: 2/26 (7.7%); radiotherapy field: nm; radiotherapy dose: nm *N* of participants hepatectomy: 26/26 (100%) *N* of participants BMT: nm *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: biochemical liver function tests (frequency of testing nm) Definition of hepatic late adverse effects: nm *N* of participants hepatic late adverse effects at end of follow-up: 0/26 (0.0%) Risk factors: not evaluated
Notes	[a] Data of 41 participants with hepatoblastoma

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Low risk	Described study group consisted of more than 90% of the original cohort
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Well defined study group	High risk	Number of participants with hepatitis virus infection was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise

Tefft 1970

Methods	Retrospective cohort study
Participants	*N* of participants original cohort: nm *N* of participants described study group: 99 *N* of participants study group of interest: 99 *N* of participants with liver function tests: 88 Tumour: Wilms' tumour, neuroblastoma, hepatoma Time period diagnosis/treatment: nm

Tefft 1970 *(Continued)*

	Age at diagnosis: 14% < 1 yr, 56% 1-4 yr, 30% > 5 yr[a] Age at follow-up: nm F/M%: 55/45[a] BMI: nm *N* of participants hepatitis virus infection: nm *N* of participants acute liver disease: 31/51 (60.8%) abnormal liver function within 6 months following radiotherapy Follow-up duration: mean 3.9 (0.5 to 13.3) yr after end of treatment Completion of follow-up: 88.9%
Interventions	*N* of participants chemotherapy: 88/88 (100%); chemotherapy type: vincristine, actinomycin D and 5-fluorouracil; chemotherapy dose: nm *N* of participants radiotherapy involving the liver: 88/88 (100%); radiotherapy field: right lobe (n = 36), left lobe (n = 35), entire liver (n = 13), remaining liver after resection (n = 4); radiotherapy dose: < 25 Gy (n = 21), 25-35 Gy (n = 47), > 35 Gy (n = 20) *N* of participants hepatectomy: 4/88 (4.5%) *N* of participants BMT: nm *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: AST and other unspecified liver function tests (frequency of testing nm) Definition of hepatic late adverse effects: abnormal liver function tests *N* of participants hepatic late adverse effects at end of follow-up: 51/88 (58.0%) Risk factors: site of radiotherapy: 25/36 (96.4%) with right lobe irradiation abnormal liver function tests versus 16/35 (45.7%) with left lobe irradiation abnormal liver function tests versus 6/13 (46.2%) with whole liver irradiation abnormal liver function tests versus 4/4 (100%) with remaining liver irradiation abnormal liver function tests (ns); radiotherapy dose: 11/21 (52.4%) with < 25 Gy abnormal liver function tests versus 27/47 (57.4%) with 25-35 Gy abnormal liver function tests versus 12/20 (60.0%) with > 35 Gy abnormal liver function tests (ns) (univariable)
Notes	[a] Data of 115 participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 60% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account

Tefft 1970 *(Continued)*

Well defined study group	High risk	Number of participants with hepatitis virus infection was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise
Well defined risk estimation	Low risk	Chi^2 was calculated

Tomita 2011

Methods	Retrospective cohort study
Participants	*N* of participants original cohort: nm *N* of participants described study group: 51 *N* of participants study group of interest: 51 *N* of participants with liver function tests: 51 Tumour: malignant disease (n = 33): ALL, AML, CML, NHL, non-malignant disease (n = 18): AA, other Time period diagnosis/treatment: 1982-1997 Age at diagnosis: median 10.5 (0.9 to 15.9) yr at SCT Age at follow-up: median 26.6 (19.4 to 34.3) yr F/M%: 41/59 BMI: median (range) in 30 male participants: CRT + TBI: 23.0 (18.6 to 25.6) kg/m^2, TBI: 17.7 (13.5 to 21.3) kg/m^2, TAI + chemo: 19.4 (14.6 to 26.2) kg/m^2; median (range) in 21 female participants: CRT + TBI: 21.2 (17.1 to 24.2) kg/m^2, TBI: 17.1 (14.6 to 18.2) kg/m^2, TAI + chemo: 16.4 (16.1 to 16.4) kg/m^2 *N* of participants hepatitis virus infection: 2/51 (3.9%) HCV-RNA^+ (persistent HCV) *N* of participants acute liver disease: nm Follow-up duration: median 15.0 (6.7 to 24.7) yr after SCT Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: 51/51 (100%); chemotherapy type: etoposide, cyclophosphamide, busulphan, methotrexate; chemotherapy dose: nm; *N* of participants radiotherapy involving the liver: 46/51 (90.2%); radiotherapy field: thoraco-abdominal (n = 12), TBI (n = 34); radiotherapy dose: 6-12 Gy TBI; 3-10 Gy TAI *N* of participants hepatectomy: nm *N* of participants BMT: 51/51 (100%) allogeneic stem cell transplantation *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT, AST, γGT, liver biopsy (n = 4) (frequency of testing nm) Definition of hepatic late adverse effects: elevated ALT, AST, γGT

Tomita 2011 *(Continued)*

	N of participants hepatic late adverse effects at end of follow-up: 0/51 (0%) elevated liver enzymes; 4 participants had a liver biopsy (indicated after diagnosis of fatty liver by ultrasound) and were diagnosed with fatty liver Risk factors: median ALT, AST and γGT levels not significantly different between participants treated with CRT + TBI, TBI, and TAI + chemo (P> 0.05) (univariable)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding; unclear if the outcome assessors of the biopsies were blinded
Adjustment important confounders	High risk	Important prognostic factors or follow-up were not taken into account
Well defined study group	Low risk	Type of chemotherapy and number of participants with hepatitis virus infection were mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise
Well defined risk estimation	Low risk	Mean difference was calculated

Vora 2006

Methods	Prospective cohort study (originally developed as an RCT; a selected group of participants was followed up for hepatic late adverse effects)
Participants	*N* of participants original cohort: nm *N* of participants described study group: 43 with splenomegaly during chemotherapy *N* of participants study group of interest: 43 *N* of participants with liver function tests: 43 Tumour: lymphoblastic leukaemia Time period diagnosis/treatment: 1997-2002 Age at diagnosis: 1.0-18.0 yr Age at follow-up: nm F/M%: nm

Vora 2006 *(Continued)*

	BMI: nm *N* of participants hepatitis virus infection: nm *N* of participants acute liver disease: 0/43 (0.0%) abnormal liver function tests < 1 yr after end chemotherapy Follow-up duration: mean 3.3 (0.0 to 5.4) yr after end of treatment Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: 43/43 (100%); chemotherapy type: 6-thioguanine, 6-mercaptopurine, vincristine, methotrexate, L-asparaginase, prednisolone, dexamethasone (other chemotherapeutic regimens not mentioned); chemotherapy dose: 40 mg/m^2/day 6-thioguanine, 75 mg/m^2/day 6-mercaptopurine (dose other chemotherapeutic regimens not mentioned) *N* of participants radiotherapy involving the liver: nm; radiotherapy field: nm; radiotherapy dose: nm *N* of participants hepatectomy: nm *N* of participants BMT: nm *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: aminotransferases, liver biopsy (n = 10) (frequency of testing nm) Definition of hepatic late adverse effects: elevated aminotransferases *N* of participants hepatic late adverse effects at end of follow-up: aminotransferases: 6/43 (14.0%); liver biopsy: 10/10 (100%) portal fibrosis or nodular regenerative hyperplasia Risk factors: not evaluated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Unclear risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding; unclear if the outcome assessors of the biopsies were blinded
Well defined study group	High risk	Number of participants with hepatitis virus infection was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	High risk	Outcome definition was not objective and precise

Weber 1987

Methods	Prospective cohort study (originally developed as a RCT; a selected group of participants was followed up for hepatic late adverse effects)
Participants	*N* of participants original cohort: nm *N* of participants described study group: 19 *N* of participants study group of interest: 19 *N* of participants with liver function tests: 19 Tumour: ALL Time period diagnosis/treatment: 1979-1981 Age at diagnosis: range 0.7 to 17.0 yr[a] Age at follow-up: nm F/M%: 47/53[a] BMI: nm *N* of participants hepatitis virus infection: nm *N* of participants acute liver disease: 19/19 (100%) elevated ALT after 6 courses of high-dose methotrexate Follow-up duration: range 1.0 to 4.0 yr after end of treatment Completion of follow-up: 100%
Interventions	*N* of participants chemotherapy: 19/19 (100%); chemotherapy type: vincristine, L-asparaginase, daunomycin, methotrexate, prednisone, leucovorin, 6-mercaptopurine and cyclophosphamide; chemotherapy dose: a priming dose of methotrexate, 6000mg/m^2 was administered over 1 hour followed immediately by constant infusion of methotrexate, 1200 mg/m^2/hour for 23 hours. The total dose of methotrexate per course was 33,600 mg/m^2 over 24 hours. Twelve hours after completion of the methotrexate infusion, 200 mg/m^2 leucovorin was administered over 1 hour. Three hours later, leucovorin was started at doses of 12 mg/m^2 every 3 hours for 5 doses, then every 6 hours until the serum methotrexate level fell below 1 x 10^{-7}M. Six 23-week cycles of prednisone, vincristine, 6-mercaptopurine, L-asparaginase, cyclophosphamide, daunomycin, and twice weekly methotrexate (7.5 mg/m^2 during weeks 3 to 6, 10 to 13, and 17 to 20) were administered. Also high-dose 6-mercaptopurine (500 mg/m^2/day) on days 1 to 5 of each maintenance cycle was received *N* of participants radiotherapy involving the liver: nm; radiotherapy field: nm; radiotherapy dose: nm *N* of participants hepatectomy: nm *N* of participants BMT: nm *N* of participants blood transfusion: nm
Outcomes	Method of detection of hepatic late adverse effects: ALT, bilirubin, ALP (frequency of testing nm) Definition of hepatic late adverse effects: > upper limits of normal: ALT 40 IU/L, total bilirubin 0.8 mg/dL, direct bilirubin 0.3 mg/dL, ALP 180 IU/L (1 yr of age until adolescence), 260 IU/L (adolescent females), 350 IU/L (adolescent males) *N* of participants hepatic late adverse effects at end of follow-up: 0/19 (0.0%) Risk factors: not evaluated

Weber 1987 *(Continued)*

Notes	[a] Data of 36 participants with ALL

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group	Unclear risk	Unclear if described study group consisted of more than 90% of the original cohort or if it was a random sample with respect to cancer treatment
Complete follow-up assessment	Low risk	Outcome was assessed for more than 90% of the study group of interest
Blinded outcome assessor	Low risk	Unclear if blinding of outcome assessment, but the outcome measurement was not likely to be influenced by lack of blinding
Well defined study group	High risk	Number of participants with hepatitis virus infection was not mentioned
Well defined follow-up	Low risk	Length of follow-up was mentioned
Well defined outcome	Low risk	Outcome definition was objective and precise

AA: anaplastic anemia.
ALL: acute lymphoblastic leukaemia.
ALP: alkaline phosphatase.
ALT: alanine aminotransferase.
AML: acute myeloid leukaemia.
ANLL: acute non-lymphoblastic leukaemia.
AST: aspartate aminotransferase.
BMI: body mass index.
BMT: bone marrow transplantation.
CCS: childhood cancer survivors.
CML: chronic myeloid leukaemia.
CNS: central nervous system.
CRT: cranial radiotherapy.
CTCAE: common terminology criteria for adverse events.
F/M: female/male distribution.
GVHD: graft-versus-host disease.
HBsAntigen: hepatitis B antigen.
HBV: hepatitis B virus.
HCV: hepatitis C virus.
HDV: hepatitis D virus.
HL: Hodgkin lymphoma.
HSCT: haematopoietic stem cell transplantation.
JCML: juvenile chronic myeloid leukaemia.
JMML: juvenile myelomonocytic leukaemia.
MDS: myelodysplastic syndrome.
NHL: non-Hodgkin lymphoma.
na: not applicable.
nm: not mentioned.
ns: not significant.
PTT: prothrombin time.
RAEB: refractory anaemia with blast excess.
RCT: randomised controlled trial.
RIBA: recombinant immunoblotting assay.
RNA: ribonucleic acid.

RT: radiotherapy.
SAA: severe aplastic anaemia.
SCT: stem cell transplant.
SOS: sinusoidal obstruction syndrome.
TAI: thoraco-abdominal irradiation.
TBI: total body irradiation.
ULN: upper limit of normal.
uc: unclear.
yGT: gamma-glutamyltransferase.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adson 1981	Fewer than 50% aged 18 years or younger
Al-Attar 1986	Not reporting on hepatic late adverse effects
Amylon 1997	Follow-up duration unclear
Asdahl 2016	Not reporting on hepatic late effects as defined in our inclusion criteria.
Atay 2005	Not reporting on hepatic late adverse effects
Avet Loiseau 1991	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Bacigalupo 1991	Not reporting on hepatic late adverse effects
Baker 2010	Review
Baker 2010b	Impossible to differentiate between adult and childhood cancer survivors; < 50% diagnosed between 0-18 years
Balcerska 2000	Follow-up duration unclear
Bauditz 2007	Case series
Benesch 2001	Not reporting on hepatic late adverse effects according to our defined outcome measures: hepatitis virus infection
Benz-Bohm 2010	Cancer treatment unclear
Berger 2013	Not reporting on hepatic late adverse effects
Berjian 1980	No childhood cancer survivors: adult participants > 18 years
Berman 1980	Fewer than 50% aged 18 years or younger
Bernard 2014	Not reporting on hepatic late adverse effects according to our defined outcome measures: iron overload
Bernstein 1993	Not reporting on hepatic late adverse effects
Bhatia 2009	Review
Bhatia 2012	Review

Study	Reason for exclusion
Blum 2002	Not reporting on hepatic late adverse effects
Bonnesen 2018	Not reporting on hepatic late effects as defined in our inclusion criteria.
Broxson 2005	Case series
Brunet 2001	Fewer than 50% aged 18 years or younger
Carter 1997	Cancer treatment unclear
Cassady 1979	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Castellino 2010	Review
Cavo 1998	No childhood cancer survivors: adult participants > 18 years
Cesaro 1997	Liver function testing in hepatitis virus-positive participants
Chao 1993	Fewer than 50% aged 18 years or younger
Cheng 2005	No childhood cancer survivors: adult participants > 18 years
Cheuk 2008	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Chou 1996	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Christopherson 2014	Not reporting on hepatic late adverse effects
Christosova 2005	Case series
Claviez 1996	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Colsky 1955	Case series
Condren 2005	Impossible to differentiate between participants with and without potentially high-risk treatment for hepatic late adverse effects
Coura 2016	Not reporting on hepatic late effects as defined in our inclusion criteria.
Damon 2006	No childhood cancer survivors: adult participants > 18 years
De Fine Licht 2017	Not reporting on hepatic late effects as defined in our inclusion criteria.
Deeg 1986	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Delvecchio 2015	Not reporting on hepatic late effects as defined in our inclusion criteria; abstract from conference proceeding, no full-text paper found
Dibenedetto 1994	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Dunkel 1998	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Dupuis-Girod 1996	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
El-Raziky 2015	Only participants included with a HCV infection

Study	Reason for exclusion
Evans 1980	Not reporting on hepatic late adverse effects
Evans 1982	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Evans 1990	Fewer than 50% aged 18 years or younger
Evans 1993	Fewer than 50% aged 18 years or younger
Exelby 1975	Follow-up duration unclear
Fabbri 1994	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Farthing 1982	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Fink 1993	Impossible to differentiate between participants with and without potentially high-risk treatment for hepatic late adverse effects
Fiorreda 2010	Liver function testing in hepatitis virus-positive participants
Forbes 1995	Fewer than 50% aged 18 years or younger
Frickhofen 1994	Fewer than 50% aged 18 years or younger
Friedrichs 2010	Only adult cancer survivors
Gandola 2009	Not reporting on hepatic late adverse effects
Ganjoo 2006	No childhood cancer survivors: adult participants > 18 years
Ghosh 2017	Not reporting on hepatic late effects
Glick 2000	Fewer than 10 childhood cancer survivors
Gluckman 1979	Unclear if one of our defined outcome measures was tested
Goldsby 2011	Not reporting on hepatic late adverse effects according to our defined outcome measures: self-reported outcomes
Gonzalez-Crussi 1982	Not reporting on hepatic late adverse effects
Greenfield 2006	Not reporting on hepatic late adverse effects
Grill 1996	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Grosfeld 1976	Case series
Gutjahr 1980	Cancer treatment unclear
Haddy 1998	Liver function testing in hepatitis virus-positive participants
Haddy 2009	Number of participants with liver function testing unclear; unclear if one of our defined outcome measures was tested
Hadley 2002	Not reporting on hepatic late adverse effects

Study	Reason for exclusion
Halonen 2003	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Hanks 1980	Not reporting on hepatic late adverse effects
Harrison 1996	Fewer than 50% aged 18 years or younger
Hatanaka 1994	No childhood cancer survivors: adult participants > 18 years
Haupt 2004	Unclear if one of our defined outcome measures was tested
Hedrick 2004	Not reporting on hepatic late adverse effects
Hegewald 1982	Not reporting on hepatic late adverse effects according to our defined outcome measures; unclear if case series or cohort study
Henderson 2008	Case report
Hjern 2007	Not reporting on hepatic late adverse effects
Ho 2004	No childhood cancer survivors: adult participants
Hoffmann 2015	Not including potentially hepatotoxic treatments as defined in our inclusion criteria.
Hollard 1980	Fewer than 50% aged 18 years or younger
Holschneider 1977	Not reporting on hepatic late adverse effects according to our defined outcome measures: hepatitis virus infection
Horowitz 1993	Not reporting on hepatic late adverse effects
Hutter 1960	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Ingold 1965	Case series
Isaacs 2008	Not reporting on hepatic late adverse effects
Ivantes 2004	No childhood cancer survivors: adult participants
Jaffe 1975	Review
Jagannathan 2004	No childhood cancer survivors: adult participants > 18 years
Jenkins 2013	Review
Jirtle 1990	Review
Jung 2017	Not including potentially hepatotoxic treatments as defined in our inclusion criteria
Kamani 1996	Unclear if one of our defined outcome measures was tested
Kamble 2006	Review
Kaste 1999	Not reporting on hepatic late adverse effects
Kazanowska 2004	Not reporting on hepatic late adverse effects

Study	Reason for exclusion
Khouri 2002	No childhood cancer survivors: adult participants > 18 years
Kim 2000	No childhood cancer survivors: adult participants
Kopp 2012	Review
Kotz 1982	Case series
Kremens 2002	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Kudo 1996	No childhood cancer survivors
Lackner 2000	Impossible to differentiate between participants with and without potentially high-risk treatment for hepatic late adverse effects
Lackner 2007	Not reporting on hepatic late adverse effects according to our defined outcome measures: hepatitis virus infection
Ladenstein 1997	Not reporting on hepatic late adverse effects
Lee 2016	Not reporting on hepatic late effects as defined in our inclusion criteria; abstract from conference proceeding, no full-text paper found
Leonardi 2003	Cancer treatment unclear
Leung 2000	Liver function testing in hepatitis virus-positive participants
Levitt 2004	Not reporting on hepatic late adverse effects according to our defined outcome measures
Levy 2015	Not reporting on hepatic late effects as defined in our inclusion criteria.
Lindsay 2016	Not reporting on hepatic late effects as defined in our inclusion criteria; abstract from conference proceeding, no full-text paper found
Ljungman 1995	Fewer than 50% aged 18 years or younger
Locasciulli 1989	Fewer than 50% aged 18 years or younger
Locasciulli 1990a	Age of the participants unclear
Locasciulli 1990b	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Locasciulli 1991b	Fewer than 50% aged 18 years or younger
Locasciulli 1993	Liver function testing in hepatitis virus-positive participants
Locasciulli 1995	Review
Lockney 2016	Not reporting on hepatic late effects as defined in our inclusion criteria.
Lucas 2017	Not reporting on hepatic late effects as defined in our inclusion criteria.
MacDonald 2010	Review

Study	Reason for exclusion
Maggiore 1982	Not reporting on hepatic late adverse effects according to our defined outcome measures: hepatitis virus infection
Maguire 2002	Not reporting on hepatic late adverse effects
Martinez 1997	No childhood cancer survivors: adult participants > 18 years
Masera 1981	Liver function testing in hepatitis virus-positive participants
McBride 1976	Fewer than 50% aged 18 years or younger
McDonald 2010	Review
McIntosh 1977	Fewer than 10 childhood cancer survivors
McKay 1996	Fewer than 50% aged 18 years or younger
Meadows 1992	Unclear if one of our defined outcome measures was tested
Meeske 2015	Not reporting on hepatic late effects as defined in our inclusion criteria.
Mitrou 1990	Not reporting on hepatic late adverse effects
Mizumoto 2017	Not reporting on hepatic late effects as defined in our inclusion criteria
Mohammed 2017	Not reporting on hepatic late effects
Mohapatra 2016	Not reporting on hepatic late effects as defined in our inclusion criteria
Moore 1995	Not reporting on hepatic late adverse effects
Morrow 1982	Not reporting on hepatic late adverse effects
Murthy 1978	Not reporting on hepatic late adverse effects
Myers 1995	Not reporting on hepatic late adverse effects according to our defined outcome measures: hepatitis virus infection; Information on liver function reported for only one participant
Myers 2013	< 10 childhood cancer survivors included
Nagasue 1979	No childhood cancer survivors: adult participants > 18 years
Nagatoshi 1997	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Neilson 1996	Age of the participants and cancer treatment unclear
Nottage 2013	Not reporting on hepatic late adverse effects
O'Hara 1968	Not reporting on hepatic late adverse effects
Oeffinger 2006	Not reporting on hepatic late adverse effects
Orchard 2015	Not reporting on hepatic late effects as defined in our inclusion criteria.
Osborne 1980	No childhood cancer survivors: adult participants > 18 years

Study	Reason for exclusion
Oue 2015	Not reporting on hepatic late adverse effects according to our defined outcome measures: hepatitis virus infection
Ozawa 2017	Not reporting on hepatic late effects.
Pantoja 1975	No childhood cancer survivors: adult participants > 18 years
Pao 1989	Not reporting on hepatic late adverse effects
Park 2002	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Perwein 2011	Unclear if one of our defined outcome measures were tested
Poussin-Rosillo 1976	Fewer than 50% aged 18 years or younger
Pratt 1977	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Pritchard 2005	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Pui 1992	Not reporting on hepatic late adverse effects
Punyko 2005	Not reporting on hepatic late adverse effects
Puri 2006	Not reporting on hepatic late adverse effects
Rajendranath 2014	Not reporting on hepatic late adverse effects according to our defined outcome measures: hepatitis virus infection
Ravikumara 2006	Fewer than 50% off treatment for 1 year or more
Reaman 1985	Not reporting on hepatic late adverse effects
Rodriguez-Inigo 1997	No childhood cancer survivors: adult participants
Rossetti 1992	Number of participants with liver function testing unclear; liver biopsy during first year after chemotherapy (< 1 year off treatment)
Ruccione 2012	Cancer treatment unclear
Ruccione 2014	Not reporting on hepatic late adverse effects according to our defined outcome measures: iron overload
Samuelsson 1999	Not reporting on hepatic late adverse effects
Sawamura 1998	Not reporting on hepatic late adverse effects
Schaison 1980	Number of participants with liver function testing unclear
Schmidt 2010	Review
Scordo 2017	Abstract conference proceeding of study Scordo 2018.
Scordo 2018	No childhood cancer survivors.
Sekine 1998	Number of participants with liver function testing unclear

Study	Reason for exclusion
Sevinir 2003	Liver function testing in hepatitis virus-positive participants
Shah 2004	Not reporting on hepatic late adverse effects
Silverman 1997	Not reporting on hepatic late adverse effects
Sirvent 2017	Not reporting on hepatic late effects as defined in our inclusion criteria
Sivaprakasan 2011	Not reporting on hepatic late adverse effects
Skidmore 1997	No childhood cancer survivors: adult participants
Skinner 2012	Review
Smith 2012	Cancer treatment unclear
Socié 1999	Fewer than 50% aged 18 years or younger
Socié 2001	Not reporting on hepatic late adverse effects
Spunberg 1981	Not reporting on hepatic late adverse effects
Strasser 1999a	Fewer than 50% aged 18 years or younger
Strasser 1999b	Fewer than 50% aged 18 years or younger
Straus 1991	Not reporting on hepatic late adverse effects
Sudour 2009	Not reporting on hepatic late adverse effects according to our defined outcome measures
Tada 1997	Liver function testing in hepatitis virus-positive participants
Takeishi 2015	Not reporting on hepatic late effects as defined in our inclusion criteria (hepatitis C only).
Taylor 1997	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Tefft 1977	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Thomas 1988	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Tomás 2000	Fewer than 50% aged 18 years or younger
Trovillion 2018	Not reporting on hepatic late effects as defined in our inclusion criteria.
Tura 1998	No childhood cancer survivors: adult participants
Uchino 1978	Not reporting on hepatic late adverse effects
Uzel 2001	Not reporting on hepatic late adverse effects
Vaidya 2000	Not reporting on hepatic late adverse effects: acute toxicity (<1 year off treatment)
Van den Ouweland 1983	Fewer than 50% aged 18 years or younger
Van Dijk 2010	Not reporting on hepatic late adverse effects

Study	Reason for exclusion
Veneri 2003	No childhood cancer survivors: adult participants
Vergani 1982	Not reporting on hepatic late adverse effects according to our defined outcome measures: hepatitis virus infection; liver biopsy at cessation of chemotherapy (< 1 year off treatment)
Von Schweinitz 1994	Not reporting on hepatic late adverse effects
Wasserheit 1995	Fewer than 50% aged 18 years or younger
Weirich 2004	Unclear if one of our defined outcome measures was tested
Wexler 1996	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Willers 2001	Liver function testing in hepatitis virus-positive participants
Wolff 2006	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Woolfrey 1998	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Yamada-Osaki 1999	Liver function testing in hepatitis virus-positive participants
Yang 2005	Not reporting on hepatic late adverse effects
Yang 2006	Not reporting on hepatic late adverse effects
Yock 2016	Not reporting on hepatic late effects as defined in our inclusion criteria.
Yoo 2013	No consecutive group of participants
Zhou 2009	No childhood cancer survivors
Zimmermann 2002	Not reporting on hepatic late adverse effects: acute toxicity (< 1 year off treatment)
Zittoun 1985	Fewer than 50% aged 18 years or younger

HCV, hepatitis C virus

Characteristics of studies awaiting assessment *[ordered by study ID]*

Halley 2012

Methods	Cohort study
Participants	40 childhood cancer survivors (> 5 years since end of treatment) treated for stage 3 or 4 neuroblastoma
Interventions	Participants were treated with chemotherapy, radiotherapy, surgery, and/or autologous bone marrow transplantation. Specific details on cancer treatment were not reported.
Outcomes	5 out of 40 participants (12.5%) had hepatic late adverse effects > 5 years since end of treatment. 1 participant had a hepatitis C infection.
Notes	This study has not been published in full text (as of September 2018), but has been presented at the SIOP conference 2012. From currently available data it is unclear if this study is eligible for inclusion in this review.

Kovacs 2007

Methods	Cohort study
Participants	138 children (78 boys, 60 girls) aged 1-18 years (mean 7.7) with acute leukaemia and non-Hodgkin lymphoma
Interventions	Participants were treated with chemotherapy. Specific details on cancer treatment were not reported.
Outcomes	12.1% had elevated ALT and 3.0% elevated γGT at a follow-up of 1-4 years after the end of treatment. 8.2% had elevated ALT and 0.0% elevated γGT at a follow-up > 5 years after the end of treatment.
Notes	This study has not been published in full text (as of September 2018), but has been presented at the SIOP conference 2007 (abstract PL.004). From currently available data, it is unclear if this study is eligible for inclusion in this review.

Kristinsson 2002

Methods	Cohort study
Participants	20 childhood cancer survivors treated for leukaemia. Age at diagnosis ranged from 0.4 to 13.8 years, mean age at follow-up was 16.7 years and mean time since end of treatment was 8.3.
Interventions	Participants were treated with chemotherapy (n = 20), BMT (n = 3) and TBI (n = 1).
Outcomes	1 participant (5.0%) had elevated γGT and 1 participant (5.0%) had elevated γGT and AST as well.
Notes	This study was written in Icelandic. At this moment we are awaiting the translation.

Lee 2014

Methods	Cohort study
Participants	44 adolescent survivors of childhood cancer. Median age 14.9 years (range 10 to 19.8 years) and median follow-up time elapsed after off-therapy 7.4 years (range 5 to 16.5 years). Fatty liver was evaluated by ultrasound examinations during follow-up period.
Interventions	Not mentioned
Outcomes	Fatty liver was identified in 8 survivors (18.2%).
Notes	This study has not been published in full text (as of September 2018), but has been presented at the SIOP conference 2014 (abstract EP-238). From currently available data it is unclear if this study is eligible for inclusion in this review.

Meneghello 2016

Methods	Cohort study.

Meneghello 2016 *(Continued)*

Participants	120 children treated for Wilms tumour. Clinical and laboratory features of hepatotoxicity (VOD was defined according to the McDonald criteria) and the histopathological abnormalities detected in the liver biopsy performed during nephrectomy following the preoperative chemotherapy. Long term liver function was evaluated.
Interventions	Treated according to SIOP93-01 or 2001 protocols
Outcomes	VOD occurred in 10% of children with Wilms tumour. Long term liver function was normal 0.5 to 18 years after the end of treatment (median follow-up 6.5 years).
Notes	This study has not been published in full text (as of September 2018), but has been presented at the SIOP conference 2016 (abstract P-0760). From currently available data it is unclear if this study is eligible for inclusion in this review.

Thavaraj 2006

Methods	Cohort study.
Participants	200 paediatric cancer survivors (165 boys, 35 girls) aged 1.3-30 years (mean 9.5) at follow-up with various tumours.
Interventions	52 participants were treated with radiotherapy. Specific details on cancer treatment are not reported.
Outcomes	14 participants had chronic liver disease and were HBsAntigen^{+} at a median follow-up of 2.5 years.
Notes	This study has not been published in full text (as of September 2018), but has been presented at the SIOP conference 2006 (abstract PJ.032). From currently available data it is unclear if this study is eligible for inclusion in this review.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMT, bone marrow transplantation; γGT, gamma-glutamyl transferase; TBI, total body irradiation.

ADDITIONAL TABLES

Table 1. Risk of bias assessment criteria for observational studies

	Internal validity	External validity
Study group	Selection bias (representative: yes/no) • if the described study group consisted of more than 90% of the original cohort of childhood cancer survivors • *or* if it was a random sample with respect to the cancer treatment	Reporting bias (well defined: yes/no) • if the type of chemotherapy and/or location of radiotherapy was mentioned • *and* if the number of participants with chronic viral hepatitis was mentioned
Follow-up	Attrition bias (adequate: yes/no) • if the outcome was assessed for more than 90% of the study group of interest (++) • *or* if the outcome was assessed for 60% to 90% of the study group of interest (+)	Reporting bias (well defined: yes/no) • if the length of follow-up was mentioned

Table 1. Risk of bias assessment criteria for observational studies *(Continued)*

Outcome	Detection bias (blind: yes/no) • if the outcome assessors were blinded to the investigated determinant (if outcomes are biochemical measurements produced by a machine, blinding of the investigator is not relevant)	Reporting bias (well-defined: yes/no) • if the outcome definition was objective and precise, i.e. if the upper limits of normal for liver function tests were described in the definition of hepatic late adverse effects
Risk estimation	Confounding (adjustment for other factors: yes/no) • if important prognostic factors (i.e. age, gender, co-treatment) or follow-up were taken adequately into account	Analyses (well-defined: yes/no) • if a relative risk, odds ratio, attributable risk, linear or logistic regression model, mean difference or Chi^2 was calculated

Table 2. Prevalence of hepatic late adverse effects in studies with an outcome definition of ALT above the upper limit of normal

Study	Total number of participants with hepatic late adverse effects	Total number of participants	Prevalence [95% Confidence Interval]
Aricò 1994	22	102	21.57 [14.70, 30.50]
Bessho 1994	2	25	8.00 [2.22, 24.97]
French 2012	2	23	8.70 [2.42, 26.80]
Green 2019	1137	2751	41.33 [39.50, 43.18]
Locasciulli 1997a	33	114	28.95 [21.42, 37.85]
Locasciulli 1997b	28	53	52.83 [39.66, 65.62]
Mulder 2013	118	1362	8.66 [7.28, 10.28]
Skou 2014	6	104	5.77 [2.67, 12.02]

ALT: alanine aminotransferase.

Table 3. Prevalence of hepatic late adverse effects in studies with an outcome definition of AST above the upper limit of normal

Study	Total number of participants with hepatic late adverse effects	Total number of participants	Prevalence [95% Confidence Interval]
French 2012	3	23	13.04 [4.54, 32.13]
Skou 2014	1	88	1.14 [0.20, 6.16]

AST: aspartate aminotransferase.

Table 4. Prevalence of hepatic late adverse effects in studies with an outcome definition of ALT or AST above the upper limit of normal

Study	Total number of participants with hepatic late adverse effects	Total number of participants	Prevalence [95% Confidence Interval]
Bresters 2008	53	216	24.54 [19.28, 30.69]

ALT: alanine aminotransferase.
AST: aspartate aminotransferase.

Table 5. Prevalence of hepatic late adverse effects in studies with an outcome definition of ALT above twice the upper limit of normal

Study	Total number of participants with hepatic late adverse effects	Total number of participants	Prevalence [95% Confidence Interval]
Landier 2012	6	263	2.28 [1.05, 4.89]
Mulder 2013	12	1362	0.88 [0.50, 1.53]
Ratner 1986	9	39	23.08 [12.65, 38.34]
Rossetti 1991	43	96	44.79 [35.24, 54.75]

ALT: alanine aminotransferase.

Table 6. Prevalence of hepatic late adverse effects in studies with an outcome definition of AST above twice the upper limit of normal

Study	Total number of participants with hepatic late adverse effects	Total number of participants	Prevalence [95% Confidence Interval]
Landier 2012	6	263	2.28 [1.05, 4.89]

AST: aspartate aminotransferase.

Table 7. Prevalence of hepatic late adverse effects in studies with an outcome definition of ALT or AST above twice the upper limit of normal

Study	Total number of participants with hepatic late adverse effects	Total number of participants	Prevalence [95% Confidence Interval]
Bresters 2008	17	216	7.87 [4.97, 12.24]
Landier 2012	7	263	2.66 [1.30, 5.39]

ALT: alanine aminotransferase.
AST: aspartate aminotransferase.

Table 8. Prevalence of hepatic late adverse effects in studies with an outcome definition of γGT above the upper limit of normal

Study	Total number of participants with hepatic late adverse effects	Total number of participants	Prevalence [95% Confidence Interval]
Mulder 2013	68	1295	5.25 [4.16, 6.60]

γGT: gamma-glutamyl transferase.

Table 9. Prevalence of hepatic late adverse effects in studies with an outcome definition of γGT above twice the upper limit of normal

Study	Total number of participants with hepatic late adverse effects	Total number of participants	Prevalence [95% Confidence Interval]
Mulder 2013	12	1295	0.93 [0.53, 1.61]

γGT: gamma-glutamyl transferase.

Table 10. Prevalence of hepatic late adverse effects in studies with an outcome definition of ALP above the upper limit of normal

Study	Total number of participants with hepatic late adverse effects	Total number of participants	Prevalence [95% Confidence Interval]
French 2012	1	23	4.35 [0.77, 20.99]
Skou 2014	11	99	11.11 [6.32, 18.81]

ALP: alkaline phosphatase.

Table 11. Prevalence of hepatic late adverse effects in studies with an outcome definition of bilirubin above the upper limit of normal

Study	Total number of participants with hepatic late adverse effects	Total number of participants	Prevalence [95% Confidence Interval]
French 2012	2 abnormal unconjugated bilirubin	23	8.70 [2.42, 26.80]
French 2012	0 abnormal conjugated bilirubin	23	0
Landier 2012	3 abnormal total bilirubin	263	1.14 [0.39, 3.30]
Skou 2014	1 abnormal bilirubin	104	0.96 [0.17, 5.25]

Table 12. Risk factors from multivariable analyses that increase the risk of hepatic late adverse effects

Study	Outcome definition ALT	Risk factor	Effect size	Significant (+/-)

Table 12. Risk factors from multivariable analyses that increase the risk of hepatic late adverse effects *(Continued)*

Green 2019	ALT > ULN	Radiotherapy involving liver treated to ≥ 15 Gy per 10% volume increase	RR 1.06 (95% CI 1.03 to 1.08)	+
Mulder 2013	ALT > ULN	Radiotherapy involving liver yes vs no	OR 2.34 (95% CI 1.07 to 5.13)	+
Green 2019	ALT > ULN	Busulfan yes vs no	RR 1.54 (95% CI 1.02 to 2.33)	+
Mulder 2013	ALT > ULN	Busulfan yes vs no	OR 3.09 (95% CI 0.29 to 32.90)	-
Green 2019	ALT > ULN	Thioguanine yes vs no	RR 1.38 (95% CI 1.02 to 1.85)	+
Mulder 2013	ALT > ULN	Thioguanine yes vs no	OR 1.40 (95% CI 0.38 to 5.18)	-
Mulder 2013	ALT > ULN	Mercaptopurine yes vs no	OR 0.84 (95% CI 0.36 to 1.99)	-
Mulder 2013	ALT > ULN	Methotrexate yes vs no	OR 1.22 (95% CI 0.53 to 2.84)	-
Mulder 2013	ALT > ULN	Dactinomycin yes vs no	OR 0.71 (95% CI 0.29 to 1.76)	-
Mulder 2013	ALT > ULN	Other chemotherapeutics (other antimetabolites, other cytotoxic antibiotics, other alkylating agents, plant alkaloids, other chemotherapeutic agents) yes vs no	Not significant	-
Green 2019	ALT > ULN	Hepatic surgery yes vs no	RR 1.90 (95% CI 1.45 to 2.49)	+
Mulder 2013	ALT > ULN	Liver resection yes vs no	OR 1.87 (95% CI 0.38 to 9.07)	-
Green 2019	ALT > ULN	BMI ≥ 25 vs < 25	RR 1.60 (95% CI 1.42 to 1.81)	+
Mulder 2013	ALT > ULN	Higher BMI z-score	OR 1.67 (95% CI 1.37 to 2.03)	+
Mulder 2013	ALT > ULN	Alcohol intake of > 14 units per week vs none	OR 2.53 (95% CI 1.04 to 6.18)	+
Mulder 2013	ALT > ULN	Alcohol intake of 7-14 units per week vs none	OR 0.87 (95% CI 0.33 to 2.31)	-
Mulder 2013	ALT > ULN	Alcohol intake of < 7 units per week vs none	OR 1.21 (95% CI 0.63 to 2.30)	-
Green 2019	ALT > ULN	Hepatitis C grade ≥ 1 vs grade < 1	RR 1.76 (95% CI 1.52 to 2.02)	+
Green 2019	ALT > ULN	Older age at evaluation per year	RR 1.01 (95% CI 1.00 to 1.01)	+
Mulder 2013	ALT > ULN	Longer follow-up time since primary cancer diagnosis per year	OR 1.10 (95% CI 1.05 to 1.15)	+
Mulder 2013	ALT > ULN	Older age at primary cancer diagnosis per year	OR 1.06 (95% CI 1.00 to 1.13)	-
Mulder 2013	ALT > ULN	Gender female vs male	OR 1.18 (95% CI 0.67 to 2.08)	-
Green 2019	ALT > ULN	Metabolic syndrome yes vs no	RR 1.40 (95% CI 1.26 to 1.55)	+
Green 2019	ALT > ULN	Statins (atorvastatin, rosuvastatin, simvastatin) yes vs no	RR 1.20 (95% CI 1.02 to 1.42)	+

Table 12. Risk factors from multivariable analyses that increase the risk of hepatic late adverse effects *(Continued)*

Green 2019	ALT > ULN	Ethnicity non-Hispanic white vs non-Hispanic black or other	RR 1.37 (95% CI 1.18 to 1.58)	+

Study	Outcome definition γGT	Risk factor	Effect size	Significant (+/-)
Mulder 2013	γGT > ULN	Radiotherapy involving liver yes vs no	OR 5.45 (95% CI 2.51 to 11.82)	+
Mulder 2013	γGT > ULN	Busulfan yes vs no	OR 4.03 (95% CI 0.33 to 48.94)	-
Mulder 2013	γGT > ULN	Thioguanine yes vs no	OR 0.51 (95% CI 0.09 to 2.80)	-
Mulder 2013	γGT > ULN	Mercaptopurine yes vs no	OR 0.64 (95% CI0.25 to 1.64)	-
Mulder 2013	γGT > ULN	Methotrexate yes vs no	OR 0.70 (95% CI 0.27 to 1.81)	-
Mulder 2013	γGT > ULN	Dactinomycin yes vs no	OR 0.46 (95% CI 0.17 to 1.21)	-
Mulder 2013	γGT > ULN	Other chemotherapeutics (other antimetabolites, other cytotoxic antibiotics, other alkylating agents, plant alkaloids, other chemotherapeutic agents) yes vs no	Not significant	-
Mulder 2013	γGT > ULN	Liver resection yes vs no	OR 1.09 (95% CI 0.12 to 9.69)	-
Mulder 2013	γGT > ULN	Higher BMI z-score	OR 1.43 (95% CI 1.14 to 1.81)	+
Mulder 2013	γGT > ULN	Alcohol intake of > 14 units per week vs none	OR 3.04 (95% CI 1.16 to 7.96)	+
Mulder 2013	γGT > ULN	Alcohol intake of 7-14 units per week vs none	OR 1.14 (95% CI 0.43 to 3.01)	-
Mulder 2013	γGT > ULN	Alcohol intake of < 7 units per week vs none	OR 0.96 (95% CI 0.48 to 1.93)	-
Mulder 2013	γGT > ULN	Longer follow-up time since primary cancer diagnosis per year	OR 1.13 (95% CI 1.07 to 1.18)	+
Mulder 2013	γGT > ULN	Older age at primary cancer diagnosis per year	OR 1.08 (95% CI 1.01 to 1.15)	+
Mulder 2013	γGT > ULN	Gender female vs male	OR 0.71 (95% CI 0.38 to 1.31)	-

ALT: alanine aminotransferase.
BMI: body mass index.
ULN: upper limit of normal.
γGT: gamma-glutamyl transferase.

Table 13. Risk factors from univariable analyses that increase the risk of hepatic late adverse effects

Study	Outcome	Risk factor	Significant (+/-)
Aricò 1994	ALT > ULN	Chronic HCV infection	+
Ballauff 1999	Liver function tests > ULN	Chronic HCV and HBV infection	+

Table 13. Risk factors from univariable analyses that increase the risk of hepatic late adverse effects *(Continued)*

Locasciulli 1983	ALT/AST > 3 x ULN	Cleared or persistent chronic HBV infection	+
Locasciulli 1983	ALT/AST > 3 x ULN	Histological diagnosis of chronic hepatitis	+
Locasciulli 1991a	ALT > ULN	Chronic HCV infection	+
Locasciulli 1997a	ALT > ULN	Chronic HCV infection	+
Rossetti 1991	ALT > 2 x ULN	Chronic HBV-HDV co-infection	+
Rossetti 1991	ALT > 2 x ULN	Chronic HBV infection	+
Hudson 2013	ALT/AST/bilirubin > ULN	High-risk treatment exposure (mercaptopurine, thioguanine, and/or radiotherapy involving the liver)	-
Gunn 2016	Elevated ALT/AST; no cut-off mentioned	Cranial radiotherapy	+
Tefft 1970	Abnormal liver function tests; no cut-off mentioned	Radiotherapy field (right lobe, left lobe, entire liver, remaining liver)	-
Tefft 1970	Abnormal liver function tests; no cut-off mentioned	Radiotherapy dose (< 25 Gy, 25-35 Gy, > 35 Gy)	-
Tomita 2011	Elevated ALT/AST/γGT; no cut-off mentioned	Treatment (CRT with TBI, TBI, TAI with chemotherapy)	-
El-Rashedy 2017	Mean ALT, AST, total bilirubin, direct bilirubin values	Standard-dose asparaginase vs low-dose	+
Bresters 2008	ALT/AST > ULN	Conditioning regimen (cyclophosphamide with TBI/TAI, cyclophosphamide with busulphan, other)	-
Bresters 2008	ALT/AST > ULN	Older age at HSCT	+
Bresters 2008	ALT/AST > ULN	Diagnosis of benign haematological disease	+
Bresters 2008	ALT/AST > ULN	Gender	-
Bresters 2008	ALT/AST > ULN	HSCT donor type (matched sibling donor, other)	-
Bresters 2008	ALT/AST > ULN	Haematopoietic stem cell source (bone marrow, autologous peripheral blood, cord blood)	-
Bresters 2008	ALT/AST > ULN	Early post-transplant morbidity (viral reactivation, VOD, acute GVHD)	-
Gunn 2016	Elevated ALT/AST; no cut-off mentioned	Overweight	+
Chotsampancharoen 2009	Mean ALT, total bilirubin values	Iron overload (high serum ferritin)	+
El-Rashedy 2017	Mean ALT, AST, total bilirubin, direct bilirubin values	Iron overload (high serum ferritin)	-

Table 13. Risk factors from univariable analyses that increase the risk of hepatic late adverse effects *(Continued)*

Schempp 2016	Elevated ALT/AST/bilirubin; no cut-off mentioned	Iron overload (high serum ferritin)	-
Hyodo 2012	Elevated γGT; no cut-off mentioned	Fatty liver	+
Hyodo 2012	Elevated ALT/AST; no cut-off mentioned	Fatty liver	-
Delvecchio 2017	Mean ALT, AST, γGT values	Fatty liver	-

+: significant.
-: not significant.
ALT: alanine aminotransferase.
AST: aspartate aminotransferase.
CRT: cranial radiotherapy.
GVHD: graft-versus-host disease.
HBV: hepatitis B virus.
HCV: hepatitis C virus.
HDV: hepatitis D virus.
HSCT: haematopoietic stem cell transplantation.
TAI: thoraco-abdominal irradiation.
TBI: total body irradiation.
ULN: upper limit of normal.
VOD: veno-occlusive disease.
yGT: gamma-glutamyl transferase.

APPENDICES

Appendix 1. Search strategy for CENTRAL

1. For **Hepatic late adverse effects** the following text words were used:

(liver fibrosis OR liver cirrhosis OR liver disease OR liver diseases OR liver diseas* OR liver dysfunction OR liver dysfunctions OR liver damage OR liver failure OR liver enzyme OR liver enzymes OR liver enzym* OR liver toxicity OR liver disfunction OR radiation-induced liver disease OR radiation induced liver disease OR RILD OR liver function test OR liver function tests OR liver insufficiency OR Hepatic Cirrhosis OR hepatic dysfunction OR hepatic dysfunctions OR hepatic cirrhosis OR hepatic failure OR hepatic function OR liver function OR radiation hepatitis OR hepatitis irradiation OR impaired liver function OR hepatic fibrosis OR hepatic fibroses OR drug induced hepatitis OR toxic hepatitis OR hepatitides OR ASAT OR ALAT OR SGPT OR SGOT OR GGT OR alanine transaminase Glutamic-Alanine Transaminase OR Glutamic Alanine Transaminase OR Alanine-2-Oxoglutarate OR Aminotransferase OR Alanine 2 Oxoglutarate Aminotransferase OR Alanine Aminotransferase OR Glutamic-Pyruvic Transaminase OR Glutamic Pyruvic Transaminase OR gamma Glutamyltransferase OR Glutamyl Transpeptidase OR GGTP OR gamma-Glutamyl Transpeptidase OR gamma Glutamyl Transpeptidase OR gammaglutamyltransferase OR Aspartate Aminotransferases OR Aspartate Apoaminotransferase OR Aspartate Transaminase OR Glutamic-Oxaloacetic Transaminase OR Glutamic Oxaloacetic Transaminase OR L-Aspartate-2-Oxoglutarate Aminotransferase OR L Aspartate 2 Oxoglutarate Aminotransferase OR Aspartate Aminotransferase OR Glutamate-Aspartate Transaminase OR Glutamate Aspartate Transaminase OR Serum Glutamic-Oxaloacetic Transaminase OR Serum Glutamic Oxaloacetic Transaminase OR hepatotoxicity OR hepatotoxic OR hepatotoxic* OR Veno-occlusive disease OR VOD OR Veno occlusive disease OR hepatic veno-occlusive disease OR Hepatic Veno-Occlusive Diseases OR Sinusoidal Obstruction Syndrome OR Hepatic Veno Occlusive Disease OR iron overload OR hemosiderosis OR siderosis OR heamosiderosis OR haemosiderosis OR Hemosideroses OR bilirubin OR bilirubins OR bilirubin* OR Bilirubin IX alpha OR Hematoidin OR Disodium Salt Bilirubin OR Monosodium Salt Bilirubin OR delta-Bilirubin OR delta Bilirubin OR Calcium Salt Bilirubin OR Calcium Bilirubinate OR albumin OR albumins OR albumin* OR prothrombin OR prothrombins OR prothrombin* OR Factor II OR Blood Coagulation Factor II OR Differentiation Reversal Factor OR Coagulation Factor II OR Alkaline phosphatase)

2. For **Survivors** the following text words were used:

(Survivor OR survivors OR Long-Term Survivors OR Long Term Survivors OR Long-Term Survivor OR survivo* OR surviving)

3. For **Childhood cancer** the following text words were used:

(leukemia OR leukemi* OR leukaemi* OR childhood ALL OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm OR acute lymphocytic leukemia)

The different searches were combined as **1** AND **2** AND **3**.

The search was performed in title, abstract or keywords.

[* =zero or more characters]

Appendix 2. Search strategy for MEDLINE (PubMed)

1. For **hepatic late adverse effects** the following MeSH headings and text words were used:

(liver fibrosis) OR (liver cirrhosis) OR (liver disease OR liver diseases OR liver diseas*) OR (liver dysfunction OR liver dysfunctions) OR (liver damage) OR (liver failure) OR (liver enzyme[all fields] OR liver enzymes[all fields] OR (liver enzym*) OR (liver toxicity) OR (liver disfunction) OR (radiation-induced liver disease OR radiation induced liver disease OR RILD) OR (liver function test OR liver function tests) OR (liver insufficiency) OR (Hepatic Cirrhosis OR Cirrhoses, Hepatic OR Cirrhosis, Hepatic OR Hepatic Cirrhoses OR Cirrhosis, Liver OR Cirrhoses, Liver OR Liver Cirrhoses OR Fibrosis, Liver OR Fibroses, Liver OR Liver Fibroses) OR (Disease, Liver OR Diseases, Liver OR Dysfunction, Liver OR Dysfunctions, Liver OR Liver Dysfunctions) OR (Function Test, Liver OR Function Tests, Liver OR Liver Function Test OR Test, Liver Function OR Tests, Liver Function) OR (Insufficiency, Hepatic OR Liver Insufficiency OR Insufficiency, Liver) OR (hepatic dysfunction) OR (hepatic dysfunctions) OR (hepatic cirrhosis) OR (hepatic failure) OR (hepatic function[all fields]) OR (liver function[all fields]) OR (radiation hepatitis) OR (hepatitis irradiation) OR (impaired liver function) OR (hepatic fibrosis OR hepatic fibroses) OR (drug induced hepatitis) OR (toxic hepatitis) OR (hepatitides) OR (ASAT OR ALAT OR SGPT OR SGOT OR GGT) OR (alanine transaminase OR Transaminase, Alanine OR Glutamic-Alanine Transaminase OR Glutamic Alanine Transaminase OR Transaminase, Glutamic-Alanine OR Alanine-2-Oxoglutarate OR Aminotransferase OR Alanine 2 Oxoglutarate Aminotransferase OR Aminotransferase, Alanine-2-Oxoglutarate OR Alanine Aminotransferase OR Aminotransferase, Alanine OR Glutamic-Pyruvic Transaminase OR Glutamic Pyruvic Transaminase OR Transaminase, Glutamic-Pyruvic) OR (gamma Glutamyltransferase OR Glutamyl Transpeptidase OR Transpeptidase, Glutamyl OR GGTP OR gamma-Glutamyl Transpeptidase OR Transpeptidase, gamma-Glutamyl OR gamma Glutamyl Transpeptidase OR gammaglutamyltransferase) OR (Aspartate Aminotransferases OR Aminotransferases, Aspartate OR Aspartate Apoaminotransferase OR Apoaminotransferase, Aspartate OR Aspartate Transaminase OR Transaminase, Aspartate OR Glutamic-Oxaloacetic Transaminase OR Glutamic Oxaloacetic Transaminase OR Transaminase, Glutamic-Oxaloacetic OR L-Aspartate-2-Oxoglutarate Aminotransferase OR Aminotransferase, L-Aspartate-2-Oxoglutarate OR L Aspartate 2 Oxoglutarate Aminotransferase OR Aspartate Aminotransferase OR Aminotransferase, Aspartate OR Glutamate-Aspartate Transaminase OR Glutamate Aspartate Transaminase OR Transaminase, Glutamate-Aspartate OR Serum Glutamic-Oxaloacetic Transaminase OR Glutamic-Oxaloacetic Transaminase, Serum OR Serum Glutamic Oxaloacetic Transaminase OR Transaminase, Serum Glutamic-Oxaloacetic) OR (hepatotoxicity OR hepatotoxic OR hepatotoxic*) OR (Veno-occlusive disease OR VOD) OR (Veno occlusive disease) OR (hepatic veno-occlusive disease OR Disease, Hepatic Veno-Occlusive OR Hepatic Veno-Occlusive Diseases OR Sinusoidal Obstruction Syndrome OR Syndrome, Sinusoidal Obstruction OR Hepatic Veno Occlusive Disease OR Veno-Occlusive Disease, Hepatic OR Veno Occlusive Disease, Hepatic) OR (iron overload OR hemosiderosis OR siderosis OR heamosiderosis OR haemosiderosis) OR (Hemosideroses OR Overload, Iron) OR (bilirubin OR bilirubins OR bilirubin* OR Bilirubin IX alpha OR Bilirubin, (4E)-Isomer OR Bilirubin, (4E,15E)-Isomer OR Hematoidin OR Bilirubin, Disodium Salt OR Disodium Salt Bilirubin OR Bilirubin, Monosodium Salt OR Monosodium Salt Bilirubin OR delta-Bilirubin OR delta Bilirubin OR Bilirubin, (15E)-Isomer OR Bilirubin, Calcium Salt OR Calcium Salt Bilirubin OR Salt Bilirubin, Calcium OR Calcium Bilirubinate OR Bilirubinate, Calcium) OR (albumin OR albumins OR albumin*) OR (prothrombin OR prothrombins OR prothrombin*) OR (Factor II OR Blood Coagulation Factor II OR Differentiation Reversal Factor OR Factor, Differentiation Reversal OR Coagulation Factor II OR Factor II, Coagulation OR II, Coagulation Factor) OR (Alkaline phosphatase)

2. For **survivors** the following MeSH headings and text words were used:

Survivor OR survivors OR Long-Term Survivors OR Long Term Survivors OR Long-Term Survivor OR Survivor, Long-Term OR Survivors, Long-Term OR survivo* OR surviving

3. For **childhood cancer** the following MeSH headings and text words were used:

(((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology)) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain

tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia lymphocytic acute) OR (leukemia, lymphocytic, acute[mh])

The different searches were combined as **1** AND **2** AND **3**.

[* = zero or more characters; mh = MeSH term]

Appendix 3. Search strategy for Embase (Ovid)

1. For **Hepatic late adverse effects** the following Emtree terms and text words were used:

1. liver fibrosis.mp. or exp Liver Fibrosis/
2. (liver disease or liver diseases or liver diseas$).mp. or exp Liver Disease/
3. (liver dysfunction or liver dysfunctions or liver disfunction).mp. or exp Liver Dysfunction/
4. (hepatic dysfunction or hepatic dysfunctions or hepatic dysfunction$).mp.
5. (liver cirrhosis or liver cirrhoses).mp. or exp Liver Cirrhosis/
6. (hepatic cirrhosis or hepatic cirrhoses).mp.
7. (liver fibroses or hepatic fibrosis or hepatic fibroses).mp.
8. (liver damage or liver insufficiency or impaired liver function or hepatic insufficiency).mp.
9. exp Radiation Injury/ or (radiation induced liver disease or radiation-induced liver disease or RILD).mp.
10. (radiation hepatitis or hepatitis irradiation).mp.
11. drug induced hepatitis.mp. or exp Toxic Hepatitis/ or toxic hepatitis.mp. or hepatitides.mp.
12. liver failure.mp. or exp Liver Failure/
13. hepatic failure.mp.
14. liver enzyme.mp. or exp Liver Enzyme/
15. (liver enzymes or liver enzym$).mp.
16. hepatic function.mp. or exp Liver Function/
17. (liver function test or liver function tests.mp. or exp Liver Function Test/
18. liver toxicity.mp. or exp Liver Toxicity/
19. (hepatotoxicity or hepatotoxic or hepatotoxic$).mp.
20. (ASAT or ALAT or SGPT or SGOT or GGT).mp.
21. (Glutamic-Alanine Transaminase or Glutamic Alanine Transaminase).mp.
22. gamma Glutamyltransferase.mp. or exp Gamma Glutamyltransferase/
23. (Glutamyl Transpeptidase or GGTP or gamma-Glutamyl Transpeptidase or gamma Glutamyl Transpeptidase or gammaglutamyltransferase).mp.
24. (Alanine-2-Oxoglutarate or alanine transaminase).mp. or exp Alanine Aminotransferase/
25. (aspartate aminotransferases or aspartate aminotransferase).mp. or exp aspartate aminotransferase/
26. (aspartate apoaminotransferase or aspartate transaminase or glutamic-oxaloacetic transaminase or glutamic oxaloacetic transaminase or L-aspartate-2-oxoglutarate aminotransferase or L aspartate 2 oxoglutarate aminotransferase or glutamate-aspartate transaminase or glutamate aspartate transaminase).mp.
27. (Aminotransferase or Alanine 2 Oxoglutarate Aminotransferase).mp.
28. (alanine aminotransferase or serum glutamic-oxaloacetic transaminase or serum glutamic oxaloacetic transaminase).mp. or exp Aspartate Aminotransferase Blood Level/
29. (Glutamic-Pyruvic Transaminase or Glutamic Pyruvic Transaminase).mp.
30. (veno-occlusive disease or veno occlusive disease).mp. or exp vein occlusion/
31. (VOD or hepatic veno-occlusive disease or hepatic veno-occlusive diseases or hepatic venoocclusive disease).mp. or exp Liver Vein Obstruction/
32. sinusoidal obstruction syndrome.mp.
33. Iron overload.mp. or exp Iron Overload/
34. (hemosiderosis or siderosis or heamosiderosis or haemosiderosis or hemosideroses).mp. or exp Liver Hemosiderosis/ or exp siderosis/
35. (bilirubin or bilirubins or bilirubin$ or bilirubin IX alpha or hematoidin or disodium salt bilirubin or monosodium salt bilirubin or delta-bilirubin or delta bilirubin or calcium salt bilirubin or calcium bilirubinate).mp. or exp Bilirubin/
36. (albumin or albumins or albumin$).mp. or exp Albumin/
37. exp Prothrombin/ or (prothrombin or prothrombins or prothrombin$ or factor II or blood coagulation factor II or differentiation reversal factor or coagulation factor II).mp.
38. Alkaline phosphatase.mp. or exp Alkaline Phosphatase/
39. or/1-38

2. For**Survivors** the following Emtree terms and text words were used:

1. (survivor or survivors or (long adj term survivor) or (long adj term survivors) or survivo$).mp.
2. survivor/ or cancer survivor/

3. surviving.mp.
4. 1 or 2 or 3

3. For **Childhood cancer** the following Emtree terms and text words were used:

1. (leukemia or leukemi$ or leukaemi$ or (childhood adj ALL) or acute lymphocytic leukemia).mp.
2. (AML or lymphoma or lymphom$ or hodgkin or hodgkin$ or T-cell or B-cell or non-hodgkin).mp.
3. (sarcoma or sarcom$ or Ewing$ or osteosarcoma or osteosarcom$ or wilms tumor or wilms$).mp.
4. (nephroblastom$ or neuroblastoma or neuroblastom$ or rhabdomyosarcoma or rhabdomyosarcom$ or teratoma or teratom$ or hepatoma or hepatom$ or hepatoblastoma or hepatoblastom$).mp.
5. (PNET or medulloblastoma or medulloblastom$ or PNET$ or neuroectodermal tumors or primitive neuroectodermal tumor$ or retinoblastoma or retinoblastom$ or meningioma or meningiom$ or glioma or gliom$).mp.
6. (pediatric oncology or paediatric oncology).mp.
7. ((childhood adj cancer) or (childhood adj tumor) or (childhood adj tumors) or childhood malignancy or (childhood adj malignancies) or childhood neoplasm$).mp.
8. ((pediatric adj malignancy) or (pediatric adj malignancies) or (paediatric adj malignancy) or (paediatric adj malignancies)).mp.
9. ((brain adj tumor$) or (brain adj tumour$) or (brain adj neoplasms) or (brain adj cancer$) or brain neoplasm$).mp.
10. (central nervous system tumor$ or central nervous system neoplasm or central nervous system neoplasms or central nervous system tumour$).mp.
11. intracranial neoplasm$.mp.
12. LEUKEMIA/ or LYMPHOMA/ or brain tumor/ or central nervous system tumor/ or teratoma/ or sarcoma/ or osteosarcoma/
13. nephroblastoma/ or neuroblastoma/ or rhabdomyosarcoma/ or hepatoblastoma/ or medulloblastoma/ or neuroectodermal tumor/ or retinoblastoma/ or meningioma/ or glioma/ or childhood cancer/
14. or/1-13

The different searches were combined as **1** AND **2** AND **3**.

[mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; / = Emtree term; $ = zero or more characters]

Appendix 4. Search strategy for conference proceedings SIOP and ASPHO

The following text words were used:

- hepatic
- liver
- hepatitis
- cirrhoses
- fibrosis
- transaminase
- sinusoidal obstruction syndrome
- veno-occlusive disease

WHAT'S NEW

Date	Event	Description
10 October 2019	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2010
Review first published: Issue 7, 2011

Date	Event	Description
16 April 2019	Amended	Contact details updated.

Date	Event	Description
1 September 2018	New citation required and conclusions have changed	Thirteen new studies were included in the update. The conclusions of the review changed accordingly. Eight studies defined hepatic late adverse effects as ALT above the upper limit of normal with prevalences ranging from 5.8% to 52.8%. One study investigated biliary tract injury defined as γGT above the upper limit of normal and reported a prevalence of 5.3%. Three studies investigated disturbance in biliary function defined as bilirubin above the upper limit of normal and reported prevalences ranging from 1.0% to 8.7%. Evidence suggests that radiotherapy involving the liver, higher BMI, chronic viral hepatitis and longer follow-up time or older age at follow-up increase the risk of hepatic late adverse effects. In addition, there may be a suggestion that busulfan, thioguanine, hepatic surgery, higher alcohol intake (>14 units per week), metabolic syndrome, use of statins and non-Hispanic white ethnicity and older age at cancer diagnosis increase the risk of hepatic late adverse effects.
9 January 2018	New search has been performed	The search for eligible studies was updated to January 2018.

CONTRIBUTIONS OF AUTHORS

Renée Mulder designed the study and wrote the protocol. She identified the studies meeting the inclusion criteria (both by initial screening and thereafter). She searched for unpublished and ongoing studies; performed the data extraction and the 'risk of bias' assessment of the included studies for both the initial review and the update; analysed the data and interpreted the results. She wrote and revised the manuscript.

Dorine Bresters critically reviewed the protocol. She identified studies meeting the inclusion criteria; checked the data extraction and performed the 'risk of bias' assessment of the included studies for the update of the review. She critically reviewed the manuscript.

Malon Van den Hof performed the data extraction and the 'risk of bias' assessment of the included studies of the initial review. She analysed the data and interpreted the results. She critically reviewed the manuscript.

Bart Koot critically reviewed the protocol. He identified studies meeting the inclusion criteria and contributed to the interpretation of the results. He critically reviewed the manuscript.

Sharon Castellino critically reviewed the manuscript.

Yoon Loke critically reviewed the protocol and the manuscript.

Piet Post critically reviewed the protocol. He identified studies meeting the inclusion criteria of the initial review. He critically reviewed the manuscript.

Aleida Postma critically reviewed the protocol. She identified studies meeting the inclusion criteria of the initial review. She critically reviewed the manuscript.

László Szőnyi identified studies meeting the inclusion criteria for the update of the review; checked the data extraction, and performed the 'risk of bias' assessment of the included studies for the update of the review. He critically reviewed the manuscript.

Gill Levitt identified studies meeting the inclusion criteria for the update of the review; checked the data extraction and performed the 'risk of bias' assessment of the included studies for the update of the review. She critically reviewed the manuscript.

Edit Bardi identified studies meeting the inclusion criteria for the update of the review; checked the data extraction and performed the 'risk of bias' assessment of the included studies for the update of the review. She critically reviewed the manuscript.

Roderick Skinner identified studies meeting the inclusion criteria for the update of the review and contributed to the interpretation of the results. He critically reviewed the manuscript.

Elvira van Dalen designed the study and critically reviewed the protocol. She identified studies meeting the inclusion criteria; performed third party arbitration, and contributed to the interpretation of the results. She critically reviewed the manuscript.

All authors approved the final version.

DECLARATIONS OF INTEREST

Renée Mulder, Leontien Kremer, Elvira van Dalen, and Bart Koot are authors of one study included in this systematic review. Dorine Bresters is an author of two studies included in this systematic review.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title of this systematic review. The title of the protocol was 'Hepatic late adverse effects after treatment for childhood cancer'. The new title is 'Hepatic late adverse effects after antineoplastic treatment for childhood cancer'.

In the protocol, it was stated that all study designs, except case reports and case series, examining the effect of treatment for childhood cancer on hepatic late adverse effects would be included. However, we also excluded studies including fewer than 10 participants.

In addition, in the protocol, it was stated that studies with a maximum follow-up of one year or less would be excluded and if no follow-up time after the end of treatment was stated, more than 90% of the study group should have been off treatment. However, we decided to only include studies in which more than 50% of the study group was off treatment for at least one year to ensure that we would analyse late adverse effects and not acute toxicity.

Also, we adapted the 'risk of bias' assessment criteria for an adequate follow-up and a well-defined outcome. The definition of a low risk of follow-up bias was as follows: if the outcome was assessed at the end date of the study for 60% to 90% of the study group or if the outcome was assessed for more than 90% of the study group, but with an unknown end date. Since there is not a straightforward definition for the end date of the study, we decided to change this 'risk of bias' item. The new definition of a low risk of follow-up bias is as follows: if the outcome was assessed for more than 90% of the study group of interest (++) or if the outcome was assessed for 60% to 90% of the study group of interest (+). In the protocol, we had not yet specified the definition of a well-defined outcome. The definition is as follows: if the outcome definition was objective and precise, that is, if the upper limits of normal for liver function tests were described in the definition of hepatic late adverse effects.

For the update of this review, we have interpreted detection bias differently. The outcome measurement, biochemically measured liver enzymes, is not likely to be influenced by a lack of blinding. In the cases that blinding was not reported and biochemically measured liver enzymes were the only outcomes in the studies, we assessed this as low risk of detection bias.

For the update of this review, we have also scanned the conference proceedings of the American Society of Pediatric Hematology/Oncology (ASPHO) (from 2013 to 2018) electronically.

In the protocol, it was stated that we planned to conduct a multivariable linear meta-regression analysis to examine the relationship between potential predictive factors and hepatic late adverse effects. Because studies lacked important data on potential predictive factors (that is, treatment characteristics, age at diagnosis, age at treatment), we were not able to perform this analysis.

After the publication of the first version of this review, Cochrane Childhood Cancer changed its policy regarding the calculation of prevalence and the corresponding 95% confidence intervals. Therefore, instead of using the generic inverse variance function of Review Manager 5 to calculate the 95% confidence intervals, we were advised to use the Wilson method. As this was not possible in Review Manager 5, we used the following tool: http://epitools.ausvet.com.au/content.php?page=CIProportion. As it was not possible to calculate the I^2 statistic, this had to be omitted from the heterogeneity assessment of included studies. In the protocol, it was stated that we would use the statistical software Comprehensive Meta Analysis, but this was no longer necessary.

FInally, in the update of this review, the data extraction was not performed by two independent reviewers, but performed by one reviewer and checked by another reviewer.

INDEX TERMS

Medical Subject Headings (MeSH)

*Chemical and Drug Induced Liver Injury; Alanine Transaminase [metabolism]; Antineoplastic Agents [*adverse effects] [therapeutic use]; Liver Diseases; Neoplasms [*drug therapy] [*radiotherapy]; Radiotherapy [*adverse effects]; gamma-Glutamyltransferase [metabolism]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant